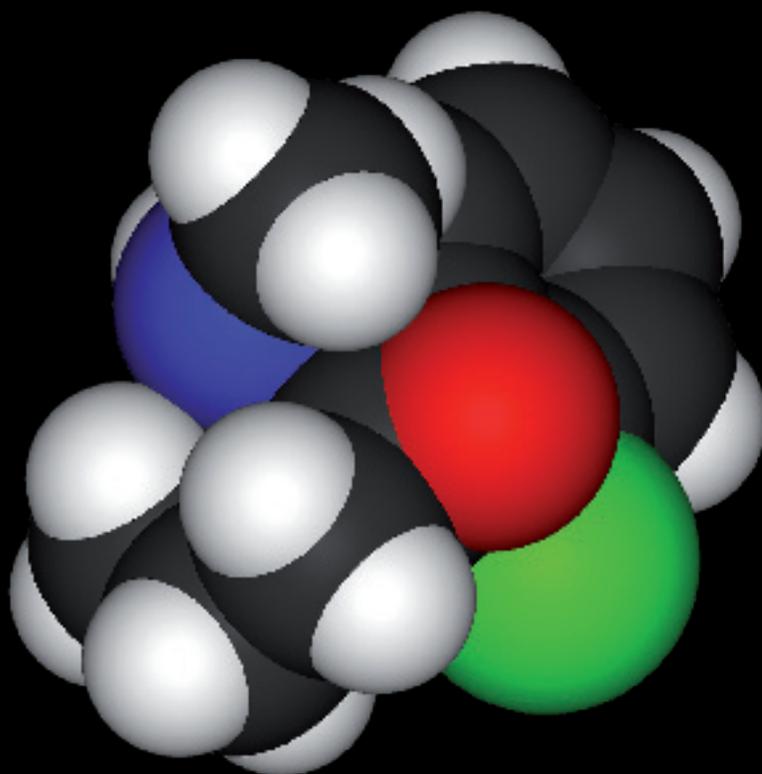


Nederlands tijdschrift voor

# anesthesiologie



volume 20,  
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## editorial

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# De wonderbaarlijke opstanding van ketamine

In dit nummer van het Nederlands Tijdschrift voor Anesthesiologie bespreken Hollmann *et al.* het perioperatieve gebruik van ketamine.<sup>1</sup> De nadruk van het overzichtsartikel ligt niet op het gebruik van ketamine als anestheticum maar als analgeticum en co-analgeticum, naast het gebruik van opioïden. Belangrijkste doel is het voorkomen van de ontwikkeling van (opioid-geïnduceerde) hyperalgesie en hieraan gekoppeld het voorkomen van chronische pijn. Dit tweede leven van ketamine heeft te maken met het specifieke werkingsmechanisme (antagonisme van het *N*-methyl-D-aspartaat (NMDA) receptorcomplex door binding aan de phenylcyclidine (PCP) bindingsposities binnen het ionkanaal) en de belangrijke rol die de NMDA receptor speelt in de verwerking en regulering van pijnsignalen. Daarnaast heeft ketamine duidelijke anti-pro-inflammatoire eigenschappen en beïnvloedt het de affectieve component van pijn.<sup>4</sup> Niet voor niets schrijven Hocking *et al.* namens de "International Association for the Study of Pain" (IASP) in een recente "Clinical Updates" KETAMINE: DOES LIFE BEGIN AT 40?<sup>2</sup> Ruim 40 jaar na zijn introductie als anestheticum is ketamine opnieuw, zoals mijn zoon zegt, *vet cool* en wordt niet alleen binnen de perioperatieve setting maar ook voor tal van specifieke aandoeningen aangewend. Soms als laatste redmiddel maar veel vaker als vermeend superieur alternatief voor bestaande therapie. Ik denk hierbij aan de behandeling van hyperalgesie/allodynie, arthritis/arthrose, migraine, perifere/centrale neuropathische pijn, fibromyalgie, het complex regionaal pijnsyndroom type 1 (CRPS<sub>1</sub>) en therapieresistente depressie. Het is duidelijk dat voordat ketamine zich mag scharen tussen de selecte groep van tijdloze geneesmiddelen (zoals morfine en aspirine) er de

noodzaak is van gedegen geblindeerd en gerandomiseerd wetenschappelijk onderzoek.<sup>2</sup> Vooral voor de behandeling van chronische pijnsyndromen is het bewijs nog onvoldoende. In het LUMC wordt op dit moment gewerkt aan het vergaren van bewijs voor de effectiviteit van ketamine in de behandeling van CRPS<sub>1</sub> en fibromyalgie. De IASP geeft aan dat op dit moment *Level I* bewijs (verkregen via systematische (meta)-analyses van gerandomiseerde klinische trials) voor de effectiviteit van ketamine slechts bestaat voor het opioïdsparend effect van *lage doses* perioperatieve ketamine toegediend via een continue iv infusie.<sup>2</sup> De verminderde opioïdconsumptie leidt in de postoperatieve fase tot minder misselijkheid en braken en gaat met slechts minimale psychomimetische bijwerkingen gepaard. Daarnaast is er voldoende bewijs dat ketamine veilig en effectief is als sedativum/analgeticum tijdens pijnlijke procedures, met name bij kinderen. *Level II* bewijs (verkregen via tenminste één goed uitgevoerde gerandomiseerde klinische trial) betreft de beschermende werking van ketamine voor het ontwikkelen van hyperalgesie, allodynie en tolerantie tijdens het gebruik van postoperatieve opioïden en daarmee verwante zaken als chronische postoperatieve pijn. Ook de behandeling van doorbraakpijn, pijn bij perifere neuropathie, ruggemergbeschadiging, fibromyalgie en migraine door ketamine vallen onder *Level II* bewijs.<sup>2</sup> Ten slotte, *Level III* bewijs (verkregen via niet-gerandomiseerde klinische trials) betreft de behandeling van fantoompijn.<sup>2</sup>

Ketamine is zeker geen wondermiddel. Er zijn aanwijzingen dat een hoge dosis ketamine een neurotoxische (apoptotische) werking heeft op het perinatale brein.<sup>3</sup> Dit is aangetoond in niet humane primaten

## editorial

en heeft geleid tot het uitdrukkelijke advies van dr. James Cottrell (hoofddirecteur van de *Journal of Neurosurgical Anesthesiology* en voormalig voorzitter van de *Society of Neurosurgical Anesthesia and Critical Care* en de ASA) in zijn "Rovenstine Memorial Lecture" tijdens de 2007 ASA meeting in San Francisco, om ketamine, maar ook de overige NMDA receptor antagonist, zoals lachgas, niet te gebruiken tijdens het laatste trimester van de zwangerschap en bij het hele jonge kind.<sup>4</sup> Bij de behandeling van acute en chronische pijn is het van belang dat ketamine naar effect en bijeffect wordt getitreerd. Bij sommige patiënten leidt een te snelle stijging van de dosis tot nare bijwerkingen (misselijkheid, depersonalisatie, hallucinaties, etc.). Doordat de bijwerkingen soms eerder optreden dan de gewilde effecten kan bij een te snelle dosisesescalatie het positieve effect van ke-

tamine verloren gaan.<sup>5</sup> Alleen in Nederland, Duitsland en Oostenrijk is de S(+) variant van ketamine geregistreerd (Ketaneest-s<sup>TM</sup>). Een duidelijke verbetering ten opzichte van het racemisch mengsel (Ketalar<sup>TM</sup>) wat betreft de bijwerkingen is er niet. Dit heeft de FDA genoopt om de S(+) variant niet toe te laten op de Amerikaanse markt. Ketamine-S<sup>TM</sup> is wel potenter (qua analgesie) dan Ketalar<sup>TM</sup>, vandaar dat de dosis circa 50% lager gekozen moet worden.

Vooralsnog wordt ketamine voor de curatieve behandeling van pijn slechts intramuraal toegepast (uitzonderingen daargelaten). Dit heeft tal van oorzaken, niet in het minst het feit dat ketamine niet vergoed wordt bij aanschaf en gebruik buiten het ziekenhuis. Blijkt uit toekomstig onderzoek dat ketamine een belangrijke rol kan spelen in de behan-

deling van chronische pijn dan zal hier zeker verandering in moeten komen. Ook zal het onderzoek zich moeten richten op alternatieve toedieningsvormen die gemakkelijk hanteerbaar zijn voor een zieke en geïnvalideerde patiënt in zijn of haar thuissituatie. Te denken valt aan iontoforetische transcutane toediening, mucosale matrixpatch en intranasale spray. Tenslotte is er ook winst te behalen in de ontwikkeling van een ketamine-alternatief met een verbeterd bijwerkingenpatroon, zowel wat betreft de psychomimetische als de cardiovasculaire bijeffecten. Ik juig de –gezien het bovenstaande niet al te wonderbaarlijke– opstanding van ketamine toe. De toekomst van ketamine –40 jaar na introductie– lijkt rooskleurig, maar.... het kan altijd nog beter.

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# Het perioperatieve gebruik van Ketamine

## *Van K naar Beter*

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**INTRODUCTIE** De ontwikkeling van postoperatieve pijn moet worden gezien als een multifactorieel proces. Er bestaat een duidelijke relatie tussen pijn, sensitivatie van het centrale zenuwstelsel (CNS) en de ontwikkeling van pijnovergevoeligheid. Een adequate perioperatieve pijnbehandeling heeft een direct effect op de overleving en de kwaliteit van leven van patiënten. Het niet-behandelen van acute postoperatieve pijn lijkt de kans op chronische postoperatieve pijnklachten te vergroten. In het verleden werd aangenomen dat een behandeling met opioïden alléén voldoende was om postoperatieve pijnklachten te voorkomen. Voortschrijdend inzicht in de rol van ontstekingsmediatoren bij de ontwikkeling van perioperatieve pijnklachten (inflammatie) heeft geleid tot het standaard toevoegen van ontstekingsremmers aan een analgetisch behandelplan. Sinds het aantonen van de rol van het mono-aminerge systeem bij het ontstaan van postoperatieve pijn vormen  $\alpha$ 2-agonisten zoals clonidine eveneens een vast onderdeel van dit behandelplan. Toch is hiermee niet alle postoperatieve pijn onder controle. Elke anesthesioloog kent in zijn eigen praktijk voorbeelden van patiënten met heftige postoperatieve pijnklachten, onvoldoende reagerend op escalerende hoeveelheden morfine. Begrippen als hyperalgesie (mogelijk opioïd geïnduceerd), tolerantie voor opioïden en de invloed van opioïden op ontstekingsreacties staan dan ook meer en meer in de belangstelling. De N-methyl-D-aspartaat (NMDA) receptor speelt een essentiële rol bij de ontwikkeling van deze hyperalgesie. Hyperalgesie betekent dat een normaal als pijnlijk ervaren prikkel door de patiënt als pijnlijker wordt ervaren. Ketamine in lage dosering, subanesthetisch en subanalgetisch, blokkeert deze NMDA receptor, resulterend in een gunstig effect op de ontstane hyperalgesie, mogelijk veroorzaakt door weefseltrauma of door toediening van opioïden.

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Dit overzicht beschrijft de plaats van lage dosering ketamine, gebruikt als adjuvans, bij een modern postoperatief pijnbeleid. Tevens wordt de pathofysiologie van onderliggende anti-hyperalgetische mechanismen beschreven.

## Ketamine farmacologie

Ketamine is een acylcyclohexylamine molecuul, een derivaat van fenylpiperidine. Ketamine werd in 1962 geïntroduceerd als een veiliger alternatief voor fencyclidine (PCP) en is al meer dan 30 jaar beschikbaar voor gebruik bij patiënten. Het ketamine molecuul bestaat als twee stereo-isomeren (S(+) en R(-) ketamine) door de aanwezigheid van een zogenaamd chiraal centrum ter plaatse van het koolstof 2-atoom van de cyclohexaanring. Oorspronkelijk, in het begin van de jaren 70, werd ketamine verkocht als intraveneus anestheticum. Nu is het vooral bekend als partydrug onder de naam "Special K." Ketamine is een niet-competitieve antagonist van de NMDA receptor<sup>2,3</sup>. Deze receptor is betrokken bij de excitatoire neurotransmissie in het centrale zenuwstelsel.<sup>4</sup> Excitatoire neurotransmitters beïnvloeden de doorgankelijkheid van celmembranen in het centraal zenuwstelsel voor calcium. Naast deze "snelle" veranderingen worden effecten op de ontwikkeling van neurale netwerken, de zgn. 'synaptic plasticity' beschreven.<sup>5</sup> De NMDA receptor onderscheidt zich van andere "ligand-gated" ion-kanalen door een aantal unieke kenmerken. Door de noodzakelijke

gelijktijdige binding van de agonist glutamaat en een co-agonist glycine zal deze receptor de kationkanalen, die sterk doorgankelijk zijn voor calcium, beïnvloeden. In fysiologische omstandigheden wordt het NMDA receptorcomplex geblokkeerd door extracellulair magnesium.

De affiniteit van de S(+) ketamine voor de NMDA receptor is vier maal groter dan die van de R(-) ketamine. Hierdoor is het S(+) ketamine bij klinisch gebruik ongeveer twee keer zo krachtig als het racemisch mengsel, en ongeveer vier keer zo krachtig als R(-) ketamine. Met dit verschil in potentie moet rekening worden gehouden bij de interpretatie van klinische studies. In dit overzicht wordt met de term ketamine het racemische mengsel bedoeld en de S(+)-enantiomeer wordt omschreven met S-Ketanest. Als ketamine wordt vergeleken met Ketanest moet de dosis door twee worden gedeeld. Op dit moment is S-Ketanest<sup>®</sup> de enige geregistreerde NMDA receptor-antagonist in Nederland die beschikbaar is voor klinisch gebruik (in de Verenigde Staten wordt enkel het racemische mengsel gebruikt)

## Ketamine – dosisafhankelijke effecten

*De hoge (anesthetische) dosering:*  
 Indien ketamine hoger wordt gedoseerd dan 1-2 mg/kg parenteraal spreekt men van een anesthesische dosering. Deze dosering wordt in dit overzicht niet besproken.

### *De analgetische dosering:*

Ketamine in een dosering rond de 0,5 mg/kg heeft een intrinsiek analgetisch effect (de analgetische dosis en wordt gebruikt als zelfstandig analgeticum (niet in combinatie met andere analgetica zoals opioïden), bijvoorbeeld bij fractuurrepositie. Bij deze dosering worden vaak psychomimetische effecten gezien waardoor het combineren met een GABA<sub>A</sub> agonist zoals een benzodiazepine noodzakelijk is. Daarnaast wordt in de literatuur beschreven dat deze dosering ketamine de opioïdconsumptie vermindert.

### *De lage (anti-hyperalgetische) dosering:*

De laatste tijd wordt vooral de lage of anti-hyperalgetische dosering van ketamine (0.5 mg/kg) geadviseerd als perioperatieve pijnstillert. Bij deze lage dosering heeft ketamine ZELF geen analgetische werking, maar potentieert het de werking van opioïd-agonisten. Daarnaast bestaat er ook een sterke anti-hyperalgetische werking. De optimale dosering van ketamine in combinatie met opioïden is beschreven door Tucker et al.<sup>6</sup> Ketamine in lage dosering (bij een plasmaspiegel van 30-120 ng/ml) heeft geen anti-nociceptieve effecten en leidt niet tot sedatie. Daarentegen worden de anti-nociceptieve effecten van fentanyl gepotentieerd. Door Suzuki et al. werd aangetoond dat lagere plasmaspiegels van ketamine (van 20 ng/ml) voldoende zijn om de pijnstilling van een epiduraal mengsel van opioïden en lokaal anestheticum te versterken na thoraxchirurgie.<sup>7</sup> Met de intraveneuze toediening van 0.24 mg/kg

## hoofdartikel

ketamine in 30 minuten wordt een plasmaspiegel van 60 ng/ml bereikt en een continue infuus 50 µg/kg/h S-(+)-Ketaneest geeft een plasmaspiegel van 20 ng/ml.<sup>8</sup> Zelfs de lage dosering van 0,0625-0,125 mg/kg ketamine is sterk anti-hyperalgetisch en heeft een gunstig effect op postoperatieve pijn, ook als andere analgetica niet effectief zijn (zoals bij hyperalgesie, opioidtolerantie en opioidonttrekingsreacties). De toediening van nog lagere dosering dan 62,5 µg/kg S-Ketaneest heeft bij klinisch gebruik geen effect<sup>9</sup>.

### Postoperatieve hyperalgesia and NMDA receptoren

Het optreden van postoperatieve pijn is een complex, multifactorieel fenomeen waarbij processen op perifeer, spinaal en supraspinaal niveau het oorspronkelijke nociceptieve signaal (somatisch, visceraal) beïnvloeden. Verschillende neurotransmitter systemen met een remmende of faciliterende invloed zijn hierbij betrokken<sup>10</sup>. Een chirurgische ingreep leidt tot perifere en centrale sensitisatie.<sup>11</sup> Weefseltrauma leidt tot perifere sensitisatie van nociceptoren (primaire hyperalgesie). Deze perifere sensitisatie draagt bij aan het ontstaan van centrale sensitisatie op spinaal niveau met de ontwikkeling van secundaire hyperalgesie. Een krachtige en aanhoudende pijnprikkel leidt tot het vrijkomen van de excitatoire neurotransmitter glutamaat waardoor NMDA receptoren worden geactiveerd. Aktivatie van NMDA receptoren faciliteert de pijntransmissie in het centrale zenuwstelsel waardoor hyperalgesie kan ontstaan. Dit is van belang omdat de gebruikelijke analgetica niet effectief zijn bij de behandeling van hyperalgesie en deze soms zelfs doen toenemen.<sup>12</sup> In de postoperatieve periode kan hyperalgesie ontstaan door sensitisatie van het zenuwstelsel door chirurgische stimuli (nociceptie-geïnduceerde hyperalgesia), maar ook door effecten van de gebruikte medicatie (medicatie geïnduceerde hyperalgesie), vooral door µ-opioidagonisten.<sup>12</sup> Wellicht is dit de reden dat een belangrijk

deel van de chirurgische patiënten inadequate pijnstilling ervaart<sup>13</sup> Er zijn sterke aanwijzingen dat het gebruik van opioidagonisten een paradoxaal effect kan hebben door een versterking van de sensitisatie voor nociceptieve stimuli.<sup>14-16</sup> Zelfs een eenmalige toediening van een opioid kan, na een aanvankelijk kortdurend pijnstillend effect, een vertraagd anti-analgetische en hyperalgetisch effect geven.<sup>17</sup> NMDA receptoren spelen hierbij een cruciale rol. Zo kan de toediening van NMDA receptor antagonist het ontstaan van opioid-geïnduceerde hyperalgesie bij proefdieren voorkomen.<sup>18,19</sup> Ook klinische studies laten zien dat de toediening van hoge dosering opioiden tijdens een operatie kan leiden tot een toename van de postoperatieve pijn.<sup>14</sup> Deze acute tolerantie voor het pijnstillende effect van postoperatieve opioiden zou dan niet zijn door een verminderde effectiviteit maar door het optreden van pijnsensitisatie. Deze "tolerantie" wordt onderdrukt door de gelijktijdige toediening van ketamine, een NMDA receptor antagonist. Dit impliceert dat de NMDA receptor betrokken is bij pijnfacilitatie.<sup>20</sup> Echter, opioid tolerantie is niet het belangrijkste probleem van opioid geïnduceerde sensitisatie.<sup>21</sup> Zorgelijker is de toename van de postoperatieve pijn bij gebruik van opioiden (dierexperimenteel<sup>22</sup> en in humane studies<sup>23,24</sup>). Er zijn sterke aanwijzingen dat de combinatie van opioid-geïnduceerde CNS sensitisatie met incisie geïnduceerde sensitisatie het pijngeheugen versterkt, wat zou bijdragen aan de ontwikkeling van chronische postoperatieve pijn.<sup>16</sup> Het is aannemelijk dat een adequate behandeling van postoperatieve hyperalgesie leidt tot een vermindering van deze toename van postoperatieve pijn.<sup>25</sup>

### Het werkingsmechanisme van de anti-hyperalgetische effecten van ketamine

NMDA receptorantagonisten hebben een analgetische werking. In tegenstelling tot opioiden zijn NMDA receptor antagonist in staat centrale overprikkelijkheid te

verminderen zonder de basale nociceptieve prikkel drempel te beïnvloeden.<sup>26</sup> Het lijkt dan ook logisch opioiden te combineren met NMDA receptorantagonisten om de perioperatieve pijnstilling te verbeteren. Uit de studies van de Kock blijkt dat de anti-hyperalgetische werking van ketamine berust op een effect op supraspinaal gelegen regelmechanismen.<sup>27</sup>

Ketamine heeft vele farmacologische effecten en beïnvloedt verschillende biologische systemen betrokken bij het ontstaan van antihyperalgesie en antinociceptie. Deze zijn niet altijd NMDA receptor afhankelijk. Ketamine heeft een agonistische werking op de opioid receptor (µ, δ, κ)<sup>28-30,33</sup> en inhibeert nicotinerge receptoren op zenuwweefsel bij klinische relevante concentraties.<sup>31</sup> Daarnaast activeert ketamine het descenderende mono-aminerge inhiberende systeem betrokken bij de modulatie van nociceptieve processen.<sup>32-34</sup> Ook worden interacties met het purinerge systeem beschreven waarbij ketaminetoediening leidt tot de release van adenosine.<sup>35</sup> Ketamine heeft lokaal anesthesische eigenschappen (blokkade van Natrium kanalen)<sup>36</sup> en heeft een effect op affectieve componenten van pijnverwerking.<sup>37</sup> Tenslotte heeft ketamine een direct ontstekingsremmend effect. Ketamine heeft een regelende werking op de inflammatoire respons en onderdrukt de productie van de pro-inflammatoire cytokines tumor necrosis factor α (TNF-α), interleukin 6 (IL-6) and interferon γ (IFN-γ).<sup>38,39</sup> Het is dan ook mogelijk dat niet de effecten op de NMDA receptor maar de anti-proinflammatoire effecten van ketamine verantwoordelijk zijn voor de anti-hyperalgetische effecten van perioperatief gebruikte ketamine.

### Synergistische effecten en afname opioid consumptie.

In een aantal "systematic reviews" is aangetoond dat het combineren van ketamine met -agonisten leidt tot een vermindering van de opioidconsumptie. Of deze combinatie ook leidt tot een betere postoperatieve pijnstilling en tot een vermindering

van de opioïdgerelateerde bijwerkingen is nog onduidelijk. In een overzichtsartikel betreffende het gebruik van subanesthetische dosering ketamine (< 1 mg/kg bolus of < 1,2 mg/kg/h) in de perioperatieve periode, leidde het combineren van ketamine met opioïden of lokaal anesthetica tot een significante verlaging van pijnscores en vermindering van de vraag om "rescue" medicatie<sup>40</sup>. Ook de intraveneuze of epidurale opioïdconsumptie neemt af na toediening van ketamine<sup>41-43</sup>. De toediening van ketamine 0.4 mg/kg ketamine (spreiding 0.1 tot 1.6 mg/kg) leidt tot een afname van 30-50 % in het gebruik van "rescue" analgetica en een gemiddelde dosisreductie van 16 mg morfine in de eerste 24 uur postoperatief. Natuurlijk blijft er discussie of deze afname in morfineconsumptie ook klinisch relevant is. In ieder geval tonen de meta-analyses een significante vermindering van postoperatieve misselijkheid en braken aan. Daarnaast is er geen (37 trials met 2385 patiënten)<sup>42</sup>, toename van de psychomimetische effecten van ketamine, indien gebruik wordt gemaakt van de lage dosering.

Ketamine wordt ook in combinatie met een opioïd gebruikt als mengsel voor intraveneuze patiënt gecontroleerde analgesie (PCA). Uit een grote enquête<sup>44</sup> blijkt dat de toepassing van een mengsel van morfine en ketamine (ratio 1:1 met een lock-out interval van 8 min) in een PCA pomp veilig is, en gepaard gaat met lage pijnscores en een hoge mate van patiënttevredenheid. Zelden treden psychomimetische effecten waardoor deze behandeling gestaakt dient te worden. Hoewel intraveneuze toediening van ketamine (doses 0.75-2 mg/ml) met morfine middels PCA pomp kan leiden tot een afname van de morfinebehoefte<sup>41</sup>, wordt dit niet door alle systematische reviews onderschreven.<sup>42</sup>

### Het antihyperalgetisch effect van ketamine

Het gebruik van ketamine in lage dosering leidt tot een belangrijke afname van de hyperalgetische zone voor mechanische prikkels rond een incisie. Deze onderdrukking

van centrale sensitizatie, als gevolg van een operatieletsel, werd al in 1997 aangetoond<sup>45</sup> bij patiënten die een nefrectomie ondergingen. Deze resultaten werden bevestigd in een recent onderzoek (colonchirurgie) waarbij<sup>27</sup> het toedienen van een lage dosis ketamine (intraveneus of epiduraal) gepaard ging met een vermindering van de hyperalgesie en een afname van postoperatieve pijnklachten tot zes maanden na operatie.

De toediening van hoge dosering remifentanyl leidt tot een toename van 50 % van de postoperatieve zone van secundaire hyperalgesie<sup>23</sup>. Door de gelijktijdige intraoperatieve toediening van een lage dosis ketamine (0.5 mg/kg bolus gevolgd door 0.3 mg/kg/h tot het sluiten van de huid waarna 0.12 mg/kg/h gedurende 48 h) kon een toename van postoperatieve secundaire hyperalgesie en morfine behoefte worden voorkomen.<sup>24</sup> Dezelfde resultaten werden gevonden door Koppert and co-workers<sup>46</sup> bij een menselijk model met elektrische hyperalgesie. Ook in een meta-analyse werd aangetoond dat het peroperatieve gebruik van lage dosering ketamine in combinatie met opiaten of lokaal anesthetica een belangrijke afname van de hyperalgetische zone rond een incisie laat zien.<sup>40</sup>

De behandeling van perioperatieve pijnklachten bij patiënten die al langdurig opioïden gebruiken is niet eenvoudig.<sup>47</sup> Het langdurig gebruik van opioïden kan leiden tot sensitizatie van het CNS voor pijn waardoor hyperalgesie- en tolerantiefenomenen ontstaan. Deze fenomenen liggen ten grondslag aan de hoge mate van postoperatieve pijn en de sterk toegenomen postoperatieve opioïd behoefte (drie tot vier keer toegenomen)<sup>14,47</sup>. Uit het beperkt beschikbare onderzoek bij deze patiëntencategorie blijkt dat de toediening van lage dosis van ketamine een gunstig effect heeft op postoperative pijn en de escalatie van opioïd-consumptie kan voorkomen. Zo bracht een ketamine bolus van 0.25 mg/kg in combinatie met titratie van morfine bij 65 % van de patiënten pijnverlichting bij wie met morfine alléén

niet voldoende pijnstilling kon worden bereikt<sup>48</sup>. Bovendien werd er een verbetering van de saturatie gezien, een afname van sufheid en een vermindering van misselijkheid en braken. In een andere studie werd gevonden dat het gelijktijdige toediening van een continu infuus met ketamine in lage dosering (0.15 mg/kg/h tot enige dagen postoperatief) bij een opioïd afhankelijke patiënt de normale pijnstillende effecten van een PCA pomp met morfine kon herstellen zonder dat er een toename van bijwerkingen werd gezien.<sup>49</sup> Wel is belangrijk dat bij deze patiënte ketamine niet in vaste verhouding met opiaten wordt aangeboden: door de relatief hoge opioïd behoefte kan anders onnodig hoge dosis ketamine worden toegediend met daarmee het optreden van ongewenste psychomimetische effecten.<sup>47</sup>

### Postoperatieve opioïd resistente pijn

Een van de meest indrukwekkende effecten van ketamine wordt gezien als het middel wordt gebruikt bij patiënten met opioïd resistente postoperatieve pijn. In een recente studie werd aangetoond dat de combinatie van 15 µg/kg morfine met 250 µg/kg ketamine (versus alleen 30 µg/kg morfine) intraveneus toegediend, leidde tot een afname in postoperatieve morfinebehoefte en significant minder pijn (ketamine groep VAS van 2.9fk1.2; morfine groep VAS van 5.5fk1.2).<sup>48</sup> Bovendien bleken in de morfine/ketamine groep slechts 9 patiënten last te hebben van misselijkheid en braken (versus 30 patiënten in de morfine groep). Deze resultaten werden bevestigd in twee andere studies<sup>50</sup>.

Samengevat vormt het gebruik van lage dosis ketamine bij opioïd resistente postoperatieve pijn een klassieke indicatie met een uitstekende kosten/baten verhouding.<sup>48</sup>

### Ketamine en epidurale Analgesia

De toediening van een lage dosering ketamine tijdens epidurale anesthesie kan een verbetering geven van de postoperatieve pijnstilling. De pijn afkomstig van de viscera en het peri-

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toneum wordt niet alleen via spinale zenuwen maar ook via de nervus vagus en phrenicus doorgegeven. Deze pijnbanen worden niet geblokkeerd gedurende een epiduraal blok waardoor centrale sensitatie en hierdoor toegenomen postoperatieve pijn toch zouden kunnen optreden. In een studie uit 2000 met patiënten die een gastrectomie moesten ondergaan, trad de meeste pijnverlichting (bij rust en bij beweging) op door de combinatie van epidurale morfine en intraveneuze ketamine. Hieruit blijkt dat ketamine een toegevoegde waarde heeft ondanks adequate epidurale pijnstilling.<sup>51</sup> Vergelijkbare resultaten werden gevonden bij twee andere studies met patiënten die respectievelijk een nieroperatie of een thoracotomie moesten ondergaan.<sup>52, 53</sup> In de laatste studie gaven de patiënten die met ketamine waren behandeld, 3 maanden postoperatief, nog steeds lage pijnscores aan en gebruikten zij minder analgetica.<sup>53</sup> In contrast hiermee kon in een andere studie bij patiënten die een nieroperatie moesten ondergaan geen meerwaarde worden aangetoond van ketamine. Wellicht werd hier een te lage dosis ketamine gebruikt (bolus 10 mg gevolgd door een continu infuus van of 10 mg/h ketamine).<sup>54</sup>

### Ketamine en orthopaedische ingrepen, invloed op het functionele herstel?

Eenmalige toediening van ketamine (0.15 mg/kg) verbetert de pijnstilling en vergroot de passieve mobilisatie van de knie na arthroscopische voorste kruisband chirurgie.<sup>55</sup> Ook verbetert het functionele herstel na kniearthroscopie in dagbehandeling.<sup>56</sup> Zelfs een lage dosering van ketamine leidt na een totale knieprothese tot een aanzienlijke pijnvermindering en sneller herstel van functie, zowel in combinatie met epidurale anesthesie<sup>57</sup> als met een continue femoraal blok.<sup>58</sup>

Echter niet alle studies zijn positief. In een studie met 30 patiënten die een arthroscopische voorste kruisbandoperatie moesten ondergaan, leidde het toedienen van S(+) Ketanest (0.5 mg/kg bolus gevolgd door een continu infuus van 0.12 mg/

kg/h tot 2 uur na de uitleiding) tot een verhoogd morfinegebruik (maar niet significant verschillend van placebo).<sup>59</sup>

### Ketamine en dagchirurgie

In dagchirurgie zijn positieve resultaten gerapporteerd met het gebruik van ketamine. Na een eenmalige ketaminegift van 75-100 µg/kg gecombineerd met morfine (50 µg/kg) werd een vermindering gezien van de morfine consumptie van ongeveer 40 % en een afname van de pijnscores van 35 %, zonder vertraging van het bereiken van ontslagcriteria. Er werden geen psychomimetische verschijnselen waargenomen, ondanks dat ketamine 15 minuten voor de uitleiding werd toegediend.<sup>60</sup>

### Ketamine en de Intensive Care patiënt

Ook de toediening van ketamine (bolus van 0.5 mg/kg waarna continue infuus van 2 µg/kg/min gedurende 24 uur gevolgd door 1 µg/kg/min gedurende de tweede 24 uur) in combinatie met morfine aan patiënten, die na een grote buikoperatie op de IC lagen, had een morfinesparend effect tot gevolg. De morfineconsumptie verminderde van 80fk37 mg naar 58fk35 mg zonder dat bijwerkingen optraden.<sup>61</sup>

### Ketamine en cardiothoracale chirurgie

Het geven van een bolus van 75 µg/kg ketamine gevolgd door een continu infuus van 75 µg/kg/h gedurende 48 uur bij patiënten die een CABG ondergaan, leidt tot een vermindering van de postoperatieve opioidconsumptie. Daarbij steeg het aantal patiënten dat de kwaliteit van postoperatieve pijnstilling beoordeelde als zeer bevredigend van 35 naar 60 %. Wel hadden vier van de patiënten last van kortdurende hallucinaties waardoor bij twee patiënten het staken van de ketamine toediening noodzakelijk was.<sup>62</sup>

### Psychotomimetic Effecten

Het gebruik van ketamine volgens het aanbevolen doseringsschema van Himmelseher and Durieux (bolus toediening in combinatie met een

laag gedoseerd infuus) gaat niet gepaard met psychomimetische effecten.<sup>201275263</sup> Toch kunnen psychomimetische effecten optreden bij gebruik van ketamine. Deze worden meestal als niet hinderlijk ervaren. Verlaging van de dosering leidt vrijwel altijd tot het verdwijnen van deze verschijnselen zonder dat het pijnstillende effect verloren gaat. De psychische verschijnselen van ketamine verdwijnen overigens snel na het staken van de toediening. Uit eigen ervaring met het gebruik van ketamine moet toch 20 % van de patiënten als non-responders worden geïdentificeerd en bij ongeveer 5 % van de patiënten moet de ketaminetoediening worden gestaakt in verband met onacceptabele bijwerkingen. Mogelijk hangt dit samen met het feit dat er grote verschillen bestaan in de noodzakelijke ketaminedosis om de NMDA receptor te onderdrukken.<sup>64</sup>

### Ketamine – toedieningsduur

Op dit moment is er nog onvoldoende kennis met betrekking tot het optimale doseringsschema van ketamine. Baserend op moderne inzichten in het ontstaan van hyperalgesie en sensitatie en de duidelijke meerwaarde van multimodale analgesie is het echter logisch om ketamine al voor de incisie op te starten en door te geven tot alle nociceptieve stimulatie verdwenen is.

### Aanbeveling voor het gebruik van ketamine

Er zijn twee indicatiegebieden te onderscheiden voor ketamine als adjuvans bij de postoperatieve pijnbestrijding:

- (1) bij grote ingrepen waarbij veel postoperatieve pijn/inflammatie en/of de ontwikkeling van een chronisch pijnsyndroom wordt verwacht zoals grote abdominale ingrepen (postoperatieve pijn, inflammatie), mastectomieën (chronisch pijnsyndroom/PONV) en thoracotomieën (chronisch pijnsyndroom, postoperatieve pijn, inflammatie), patiënten met inflammatoire darm ziekte (M.Crohn; Colitis ulcerosa)

- (2) bij patiënten bij wie met morfine onvoldoende pijnstilling wordt bereikt.

Contra-indicaties voor het gebruik van ketamine zijn: open oogwonding, ischemische hartziekten, vasculaire aneurysmata en psychiatrische ziektebeelden.

## Werkwijze

### Indicatiegebied (1):

Start toediening van S(+)-Ketanest vóór de chirurgische incisie

- Bolus: 0.25 mg/kg
- Continue infusie: 100-400 µg/kg/h S(+)-Ketanest
- Indien operatie >2 uur: stop continue infusie 30 min. voor einde ingreep

*Tip: Oplossing: 20 ml van S(+)-Ketanest 25 mg/ml (totaal: 500 mg), aangevuld met 30 ml NaCl 0.9% tot 50 ml. 1ml = 10 mg S(+)-Ketanest (kan 50 uur doorlopen zonder spuitwissel)*

### Postoperatief:

- Continueren/herstarten continue infusie in een dosering van 100 µg/kg/h S(+)-Ketanest
- Door te geven tot 48 uur postoperatief in combinatie met PCA-morfine

### Indicatiegebied (2):

- I.v. bolus 0.125 mg/kg S(+)-Ketanest, zonodig 2x herhalen

## Summary

Surgery is inevitably associated with tissue injury and inflammation. Both lead to activation of intracellular signal transduction pathways, in particular activation of kinases. Those activated kinases lead to several conformational changes finally resulting in a phosphorylation of the NMDA receptor complex. Flux of Ca<sup>++</sup> through phosphorylated NMDA receptor is markedly increased which results in further activation of kinases and receptor phosphorylation,

finally merging in sensitization and increased pain perception.

Opioids, commonly used to treat perioperative pain are best known for their antinociceptive action.

Hence much less known is their ability to induce pain via a mechanism similar to that described for tissue injury and inflammation.

S(+)-Ketanest should not be seen just as an additional drug with antinociceptive effects leading to a reduction in opioid requirement, but much more as an antihyperalgesic which is able to prevent or at least reduce the pathophysiological changes that ultimately could lead to pain states that cannot be effectively treated with opioids.

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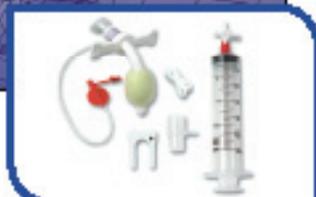
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**case report**

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# An Acute Allergic Reaction to Ultrasound Transmission Gel

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**INTRODUCTION** Ultrasonography is increasingly used in the daily anesthesiology practice. To provide an acoustic pathway between the transducer and the skin, ultrasound transmission gels are used as “couplants”. The couplant eliminates air from the interface and adapts the probe to the contours of the skin. Ultrasonic gels are thought to be harmless. However we present a case in which the application of a coupling gel led to a severe allergic reaction.

## Case Report

A 35 year old female patient, suffering acute cholecystitis, was referred to our department for the insertion of a peripheral venous line for the administration of antibiotics. Due to severe adipositas, her body mass index was 44, two nurses and two physicians were not able to insert an intravenous cannula.

After careful examination it was concluded that obtaining intravenous access was impossible with conventional techniques. Therefore we decided to insert a peripheral intravenous cannula under ultrasonographic guidance.

In sitting position and after applying an upper arm tourniquet, disinfection and application of sterile jelly, (Instillagel®, Farco-Pharma GMBH, Cologne, Germany) an ultrasound examination of the lower arm was performed using a Sonosite Micromax (Bothell, USA) equipped with a high-frequency 38 mm linear probe in the 7- to 13-MHz range. Veins accessible for the insertion of the cannula were identified in short-axis view.

Five minutes after the start of the procedure, the patient complained of pruritus and warmth at the examination site, shortness of breath and the feeling of throat swelling. She reported spontaneously that she recognized this feeling as an allergic reaction from another incident. The skin became erythematous but no urticaria developed. Anamnesis and examination of the medical record revealed that she was allergic to all amide-type local anesthetics which had been proven by intradermal testing. Immediately the skin was cleaned with water and a non-sterile ultrasound gel, (Aquasonic®, Parker Laboratories Inc, Fairfield, USA) was applied. Under ultrasonographic control an 18-gauge cannula, (BD Venflon™ Pro, Becton Dickinson, Helsingborg, Sweden), was quickly inserted without difficulty. Oxygen was administered, clemastine 1 mg and Prednisolon 50 mg were injected intravenously and adrenaline prepared.

Hemodynamic and respiratory monitoring were applied. No hemodynamic or respiratory compli-

cations occurred. The symptoms gradually disappeared and after an observation of 4 hours, she was transferred in good condition to the ward. All events and data were recorded in the patient’s medical record. The referring physician was informed about the complications.

Moreover, patient and nursing staff were instructed in case of reappearance of symptoms, to contact us immediately. No adverse events occurred at the ward.

## Discussion

Ultrasound transmission gels are a prerequisite when performing ultrasonographic examinations. Ultrasound transmission gel act as “couplant” that provides an acoustic pathway between the transducer and the skin. The couplant eliminates air from the interface and adapts the probe to the contours of the skin. The ultrasound image is formed by the reflection of sound waves. Reflection occurs when a sound wave hits a boundary between materials having different acoustic impedance. Reflection of sound by the ultrasonic gel

should be minimized because the gel acts as an acoustic window through which the image can be formed. An improper couplant match causes reflections that decrease acoustic energy transfer (just as reflections from a glass window obscure the image behind the glass).

Generally ultrasonic gels are regarded as harmless to patients but cases of contact hypersensitivity from gel application have been reported.<sup>1,2,3</sup>

Most gels contain water, carbomer thickener, preservatives, colorants and odorants. The carbomers envelop the water in a polymeric network and gives the gel a high viscosity. Hypersensitivity after mucosal contact with a gelling agent in local anesthetic has been described.<sup>4</sup>

Preservatives are required to prevent degradation and growth of pathogenic microorganisms. Preservatives like methyl and propyl paraben are effective against molds and fungi and are mostly used synergistically with bactericides. These parabens are also used as preservatives in food, cosmetics, sunscreens, shampoos, and many other products but may cause allergic skin reactions.<sup>3</sup>

Propylene glycol, or propane-1,2-diol is a diol alcohol and a colorless clear oily liquid that is frequently added to accomplish preservation as bactericide and moisturizer, but is known to be a skin sensitizer.<sup>5</sup>

Added dyes and scents may cause allergic reactions to the skin too.<sup>6</sup>

Several commercial available ultrasound gels exist. In daily practice we used Installagel®, because it was

readily available in the operating theatre where it is used as a lubricant and local analgesic for bladder catheter insertion. Moreover it can be used in sterile procedures. An Installagel-syringe contains chloorhexidine, methyl and propyl hydroxybenzoaat and 20 mg lidocaine. For ultrasonographic guidance, lidocaine is not a necessary component.

Adverse allergic reactions to lidocaine are uncommon.<sup>7</sup> Therefore an allergic reaction should be differentiated from hypersensitivity to excipients as parabens, or sodium metabisulfite in epinephrine containing solutions. The most commonly reported cause of allergic contact dermatitis to lidocaine is through the use of antihemorrhoidal preparations.<sup>8</sup>

An allergic reaction is the hypersensitive response of the immune system of an allergic individual to a substance. Anaphylaxis (severe allergic reaction) is an IgE-mediated, rapidly developing, systemic allergic reaction. IgE antibodies are released to attack the allergen and mast cells release a variety of mediators including prostaglandins, leukotrienes and histamine into the tissues and blood promoting allergic reactions. Anaphylactoid reactions result from the direct release of mast cell mediators and are not IgE mediated.

Most allergic events to local anesthetics involve contact hypersensitivity.<sup>9,10,11</sup> The amino-local anesthetics such as lidocaine have a lower sensitizing potential than amino-esters of local anesthetics.

12 Amino-esters are degraded to p-aminobenzoic acid (PABA), which is responsible for allergic reactions. But also the preservative compound methylparaben, which is frequently added to amino-amide local anesthetics, is metabolized to PABA. In the differential diagnosis for allergy to local anesthetics this should be considered and patients should be tested with preservative-free amide local anesthetics. An intradermal challenge with preservative free lidocaine had been performed in our patient and caused a severe allergic reaction.

This case illustrates that before every medical intervention, patients should be asked if they have any known allergies. The medical record should also be examined for any known allergies. Before starting an ultrasonographic examination they should be asked for allergies to cosmetics or other locally applied substances too. A sterile, hypo allergic ultrasonic gel designated solely for ultrasonographic use should be used.

#### Acknowledgement

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#### Abstract

An acute allergic reaction to ultrasonic gel is described. Due to different substances in the ultrasonic gel it is important to ask for known allergies including cosmetics or other locally applied substances. Only sterile hypo allergic gels designated for ultrasound transmission should be used.

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# Intravenous Midazolam: beware of Laryngospasm

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**SUMMARY** Midazolam is commonly prescribed for premedication or conscious sedation of patients undergoing procedures both inside and outside the operating theatre. Laryngospasm is a potentially life-threatening complication associated with its use. In this report we present a case of midazolam-induced laryngospasm and provide a brief review of the literature.

## Introduction

Laryngospasm during anesthesia is typically the result of airway maneuvers such as intubation or suctioning during light planes of anesthesia. In this report we present an anesthetic crisis resulting from an unusual case of laryngospasm triggered by administration of a low dose of midazolam.

## Case report

A 44 year old woman (66kg, ASA 1) presented for inguinal hernia repair. Preoperatively, informed consent for a spinal anesthetic combined with an ilioinguinal block had been obtained. The patient had no relevant medical history, did not use any prescription drugs, and had no known allergies. Examination of the heart, lungs and airway was unremarkable.

On arrival in the operating theatre a 20 gauge intravenous cannula was inserted and standard monitoring techniques were implemented (non-invasive blood pressure, ECG, pulse oximetry). The patient had never been operated on before, and was slightly apprehensive about the impending spinal anesthetic and surgery. Midazolam 1.5 mg iv was therefore administered.

A few minutes later while the spinal set was being prepared, the patient suddenly became very restless, agitated and dyspneic. She seemed to be choking and was unable to communicate what the problem was. With her right hand she seemed to be gesturing towards her throat and upper thoracic area. At this point the SpO<sub>2</sub> had dropped to 92%, heart rate was 90/min, and the blood pres-

sure was elevated at 150/100.

100% oxygen was immediately administered by face mask followed by a bolus of propofol 200 mg iv and sufentanil 10 micrograms iv. Following loss of the eyelash reflex the patient was easily mask ventilated. A laryngeal mask airway (LMA) was inserted and mechanical ventilation was initiated in the volume-controlled mode. Airway pressures were normal. Auscultation of the lungs revealed normal bilateral breath sounds.

Our differential diagnosis included an anxiety attack, and a reaction to the midazolam. The dyspnea, inability to speak, agitation and uncoordinated movements of the patient also suggested the possibility of inadvertent administration of a

non-depolarising muscle relaxant from a mislabelled syringe. However, train of four neuromuscular monitoring following insertion of the LMA revealed four equal twitches.

The remainder of the anesthetic was uneventful and towards the end of the surgery the patient was allowed to ventilate spontaneously. On awakening the LMA was removed. Initially the patient appeared to be somewhat dazed and disoriented. This dizziness rapidly cleared up and adequate communication with the patient was re-established.

The patient was transferred to the recovery area and later to the ward. A day later she was successfully discharged from the hospital.

## Discussion

In retrospect we believe that this was a case of midazolam-induced laryngospasm. An anxiety attack is unlikely as the patient had no history of panic attacks or other psychiatric pathology. The possibility of inadvertent administration of a muscle relaxant was excluded by the four equal twitches on the train-of-four monitor following induction. In addition, our laboratory later confirmed that the remaining fluid in the syringe was indeed pure midazolam.

An allergic reaction is also an important consideration. The specific formulation of midazolam that we use in our clinic is Dormicum® (Roche). The active ingredient of this solution is midazolam hydrochloride. The excipients are water, sodium chloride, and sodium bicarbonate. Allergic reactions involving midazolam have been described. One report describes a young woman who developed pruritis and severe facial oedema following a 2mg i.v. bolus of midazolam(1). Another report described a young child which developed periorbital oedema and a disseminated urticarial allergic reaction after receiving intranasal

midazolam for a dental procedure (2). Although laryngospasm may be a manifestation of an allergic reaction, our patient did not reveal any other symptoms or signs characteristic of an allergic reaction. She did not develop any external manifestations such as urticaria, rash or oedema. Auscultation of the lungs following intubation revealed normal bilateral breath sounds and no wheezing suggestive of bronchospasm. In addition she remained hemodynamically stable throughout the entire procedure with no need for vasopressors. We therefore consider an allergic reaction unlikely.

In the Dutch pharmacological formulary(3), laryngospasm is listed as a rare complication of midazolam. In a safety and efficacy study with midazolam (Versed®) involving 397 pediatric patients an overall incidence of laryngospasm of 2% was observed (4).

The anatomical and physiological basis of laryngospasm has been reviewed elsewhere (5). In the literature a variety of triggers of laryngospasm have been described. In the perioperative setting laryngospasm typically results from laryngeal stimulation during "light" anesthesia. Stimulating factors include airway instrumentation and the presence of blood or secretions in the pharynx. In patients with gastroesophageal reflux disease (GERD) acid reflux may also precipitate laryngospasm. In fact recurrent laryngospasm may be the only manifestation of GERD in some patients (6).

Another mechanism of laryngospasm involves visceral nerve stimulation (7). For example peritoneal traction during surgery can induce laryngospasm. Similarly stimulation of visceral nerves in the pelvis or thorax during surgery may induce laryngospasm if the patient is not "deep" enough.

Other potential triggers of laryngospasm include electrolyte disor-

ders (specifically hypocalcemia (8) and hypomagnesemia (9)), and use of certain drugs. A variety of drugs used in the perioperative setting have been associated with laryngospasm, for example ketamine (10), fentanyl (11) and dopamine antagonists (12) such as haloperidol and metoclopramide.

Concerning midazolam-induced laryngospasm we identified one report in the emergency medicine literature. Davis et al described a case similar to ours in which a patient received midazolam 3mg iv for cardioversion and subsequently developed laryngospasm that was successfully controlled with flumazenil(13). In our case we believe that the laryngospasm was relieved by the bolus of propofol that was administered. Successful relief of extubation laryngospasm by propofol has been described in both pediatric(14) and obstetric(15) patients emerging from anesthesia. We used an induction dose of propofol, but subhypnotic doses of propofol (0.25-0.8mg/kg) also appear to be adequate(14,15).

In summary, midazolam is commonly used by anesthesiologists as well as non-anesthesiologists as an anxiolytic or sedative for patients undergoing a variety of medical procedures. Potential side effects such as paradoxical reactions or airway obstruction following excessive doses for conscious sedation are generally well known. Laryngospasm is a rare and less well known complication. Physicians using midazolam need to be aware of this potentially life-threatening complication and be prepared to treat it. Midazolam-induced laryngospasm may be successfully terminated with either flumazenil or subhypnotic doses of propofol. If these pharmacological maneuvers are unsuccessful measures to secure the airway and adequately oxygenate the patient may be necessary.

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# Sugammadex, a new topic in neuromuscular management

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**ABSTRACT** Steroidal neuromuscular blocking agents, such as rocuronium, are widely used in clinical anesthesia and emergency medicine to facilitate endotracheal intubation and artificial ventilation and to allow surgical access to body cavities. Reversal of neuromuscular blockade is important for the acceleration of patient's recovery and prevention of postoperative residual neuromuscular blockade and reduces the incidence of severe morbidity and mortality associated with anesthesia management. Sugammadex is the first selective relaxant binding agent (SRBA) and has been designed to reverse the steroidal neuromuscular blocking drug rocuronium. Encapsulation of the rocuronium molecule by sugammadex results in a rapid decrease in free rocuronium in the plasma and subsequently at the nicotinic receptor at the motor endplate. After encapsulation, rocuronium is not available to bind to the nicotinic receptor in the neuromuscular junction. This promotes the liberation of acetylcholine receptors, and muscle activity reappears. This new concept of reversal of neuromuscular blockade induced by rocuronium led to impressive results in animal and phase 1 and 2 studies. Sugammadex is currently in phase 3 clinical studies and may be commercially available by 2008.

**SAMENVATTING** Steroidale spierverslappers zoals rocuronium worden zeer frequent toegepast in de klinische anesthesiologie en spoedeisende geneeskunde, om endotracheale intubatie en kunstmatige ademhaling mogelijk te maken en chirurgische ingrepen te faciliteren. Aan het eind van een algehele anesthesie, waarbij spierverslapping is toegepast, is het van essentieel belang dat de spierfunctie is genormaliseerd, om co-morbiditeit, gerelateerd aan het gebruik van spierverslappers, te voorkomen. Het antagoneeren van spierrelaxantia, om dit herstel te bespoedigen wordt in de huidige klinische praktijk gerealiseerd met cholinesteraseremmers, zoals neostigmine en pyridostigmine. Deze gaan echter gepaard met systemische muscarine cholinerge bijwerkingen en zijn niet voldoende werkzaam bij diepe neuromusculaire blokkade. Sugammadex is een gemodificeerde  $\gamma$ -cyclodextrine dat rocuronium bindt met een zeer hoge affiniteit (107 M<sup>-1</sup>). Deze binding resulteert in snelle daling van vrij rocuronium in plasma en aansluitend in het effectcompartiment, de nicotinerge acetylcholine receptor in de neuromusculaire overgang. Dit leidt tot een veilig, snel en volledig herstel van rocuronium-geïnduceerde spierverslapping binnen enkele minuten, ongeacht de diepte van de neuromusculaire blokkade. Sugammadex heeft tot indrukwekkende resultaten geleid in zowel dierexperimenteel als in humane experimenten in fase 1 en 2 studies. De ontwikkeling van sugammadex is nu in fase 3 klinische studies en sugammadex zal naar verwachting in 2008 commercieel beschikbaar zijn.

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## KEY WORDS

neuromuscular blocking agents, sugammadex, reversal agents, postoperative residual curarization

## Introduction

Steroidal neuromuscular blocking agents (NMBAs), such as rocuronium, are widely used in clinical anesthesia and emergency medicine to facilitate endotracheal intubation and artificial ventilation and to allow surgical access to body cavities.<sup>1</sup> Although the use of NMBAs has significantly reduced the incidence of laryngopharyngeal lesions due to endotracheal intubation, their use is still associated with higher morbidity and mortality compared with anesthetic techniques that do not use NMBAs.<sup>2-4</sup> This is mainly attributable to the development of postoperative residual neuromuscular blockade (PORC), resulting in hypoventilation, airway obstruction and hypoxia.<sup>3,4</sup> Reversal of neuromuscular blockade is important for the acceleration of patient recovery and prevention of PORC and may reduce the incidence of severe morbidity and mortality associated with anesthesia management.<sup>5</sup>

At present, the reversal of neuromuscular blockade is achieved by the administration of acetyl cholinesterase inhibitors (neostigmine, edrophonium, or pyridostigmine).<sup>6</sup> Importantly, cholinesterase inhibitors have a number of undesirable side-effects (bradycardia, bronchoconstriction, hypersalivation, abdominal cramps and nausea and vomiting)<sup>7</sup> which can be counteracted by co-administration of muscarinic antagonists (atropine or glycopyrrolate).<sup>6</sup> However, muscarinic antagonists also have side effects (blurred vision, dry mouth, and tachycardia).<sup>7,8</sup> Furthermore, due to their mechanism of action, cholinesterase inhibitors are not capable of reversing deeper levels of neuromuscular blockade.<sup>8,9</sup> Thus, there is clearly a clinical need for a new reversal agent, with minimal side effects and the capability to reverse neuromuscular blockade effectively, independently of its depth.

Sugammadex is the first selective relaxant binding agent (SRBA) and has been designed to reverse the steroidal neuromuscular blocking drug rocuronium.<sup>9-11</sup> Sugammadex, per-6-(2-carboxyethylthio)-per-6-deoxy- $\gamma$ -cyclodextrin sodium salt, is a synthetic modified  $\gamma$ -CD derivative designed to bind selectively to the steroidal rocuronium molecule (Fig 1.)<sup>9-11</sup> Cyclodextrins, a group of cyclic oligosaccharides, are ring-shaped molecules with lipophilic inner cavities and hydrophilic outer surfaces that form complexes by inclusion of specific guest molecules, such as steroids.<sup>10,12</sup> Structurally, they consist of either six ( $\alpha$ -CDs), seven ( $\beta$ -CDs) or eight ( $\gamma$ -CDs) glucose units and each type has its own characteristics.<sup>12</sup> CDs are highly water soluble, particularly  $\gamma$ -CDs compared with  $\alpha$ - and  $\beta$ -CDs and are also biologically well tolerated.<sup>10</sup> Chemically modified CDs have been used in the clinic to increase the stability, solubility, and bioavailability of an encapsulated drug, thereby *delivering* the required dose of the drug to the appropriate target sites.<sup>10</sup> The use of a modified CD to reverse a rocuronium-induced profound neuromuscular blockade, by *removing* rocuronium from the effector site, thus represents a paradigm shift from current methodology. Encapsulation of the rocuronium molecule by sugammadex results in a rapid decrease in free rocuronium in the plasma and subsequently at the nicotinic receptor at the motor endplate. This results in an increase in total plasma concentration of rocuronium. However, after encapsulation, rocuronium is not available to bind to the nicotinic receptor in the neuromuscular junction. This promotes the liberation of acetylcholine receptors, and muscle activity reappears.<sup>10,13</sup> This new concept of reversal of neuromuscular block induced by rocuronium led to impressive results in animal and phase 1 and 2 studies. Sugammadex

is currently in phase 3 clinical studies and may be available by 2008. In this article a review is given of the recent literature on sugammadex. The efficacy, safety and pharmacokinetics will be discussed.

## Preclinical results

The efficacy of sugammadex as a reversal agent was evaluated using different animal models (mouse, guinea pig, cat and Rhesus monkey). In these experiments sugammadex showed efficient reversal of NMB induced by rocuronium, vecuronium and pancuronium. Most efficient reversal was seen in the rocuronium-induced NMB followed by vecuronium and pancuronium. Sugammadex was even able to reverse a rocuronium-induced profound neuromuscular block in Rhesus monkeys.<sup>14</sup> However, sugammadex was not effective against non-steroidal NMBAs mivacurium and atracurium and succinylcholine.<sup>15</sup> Sugammadex was also significantly faster and more efficient compared with reversal of the currently used combination of neostigmine and atropine.<sup>11</sup> Sugammadex-rocuronium complexes are highly hydrophilic, and it has been demonstrated that sugammadex is excreted rapidly and dose dependently in urine of anesthetized guinea pigs.<sup>16</sup> Investigation of the influence of renal impairment on the reversibility of rocuronium-induced NMB by sugammadex showed that the effectiveness of sugammadex in reversal of NMB block was not affected by cessation of renal blood flow.<sup>17</sup> In preclinical studies no signs of residual blockade or recurarization were observed and the injection of sugammadex did not cause significant changes in heart rate or blood pressure.<sup>9-11,13-17</sup> Preclinical studies showed positive results after the treatment with sugammadex regarding the lack of residual blockade or recurarization and side-effects.

## Clinical results

### *Efficacy and safety of sugammadex*

The first human exposure of sugammadex was reported by Gijsenbergh.<sup>18</sup> Twenty-nine healthy male volunteers received either sugammadex or placebo. In the first part of the study nineteen subjects received sugammadex up to 8.0 mg/kg without administration of a neuromuscular blocking agent, demonstrating the safety of the compound. In the second part of this study the subjects were anaesthetized and received an intubation dose of 0.6 mg/kg rocuronium or placebo. This was followed by a single bolus injection of sugammadex (0.1-8.0 mg/kg). Assessment of efficacy showed a large reduction in recovery time after the treatment with sugammadex as compared with placebo. A dose of sugammadex of 8.0 mg/kg resulted in a recovery time to a train-of-four ratio of 0.9 (normal neuromuscular function) of 1 minute compared with 52 minutes for placebo. Residual blockade or recurarization were not reported. There were no adverse events and sugammadex was well tolerated in doses up to 8.0 mg/kg. In another study the capacity of sugammadex in reversing prolonged rocuronium-induced neuromuscular block was studied.<sup>19</sup> Thirty patients were anaesthetized and received rocuronium 0.6 mg/kg as an initial dose followed by increments to maintain a deep block. Neuromuscular monitoring was carried out using acceleromyography, in the train-of-four mode. After at least 2 hours of neuromuscular block, at recovery to the appearance of the second twitch of the train-of-four, the patients received either sugammadex in a dose of 0.5-6.0 mg/kg or placebo. The results showed a sugammadex dose-related decrease in recovery time to a normal neuromuscular function (train-of-four ratio 0.9) within 2 minutes. No signs of recurarization were observed and no adverse events were reported. The conclusion of this study was that the effective dose to reverse a deep and prolonged rocuronium-induced neuromuscular block appears to be 2-4 mg/kg. A further study investigated the dose-response, safety, and

pharmacokinetics of sugammadex in a dose up to 4.0 mg/kg in reversing neuromuscular block induced by 0.6 mg/kg rocuronium.<sup>20</sup> Sugammadex decreased the reversal time in a dose-dependent manner from 21.0 minutes in the placebo group to 1.1 minute in the 4.0 mg/kg sugammadex dose group. No signs of recurarization were observed and no adverse events were reported. Sugammadex enhanced renal excretion of rocuronium and was excreted unchanged in urine. Two patients experienced hypotension after the administration of 2.0 and 3.0 mg/kg sugammadex. These adverse events were considered to be possibly related to sugammadex. Reversal of high dose rocuronium (1.0 mg/kg) by sugammadex at 3 and 15 minutes after the administration of rocuronium was evaluated in a further study.<sup>21</sup> The patients were treated with either placebo or sugammadex in a dose up to 16.0 mg/kg. This study showed that a profound rocuronium-induced neuromuscular block was on average reversed within 2.5 minutes for a dose of 8.0 mg/kg sugammadex or higher. Another study investigated the capacity of sugammadex in reversing rocuronium-induced neuromuscular block with either sevoflurane or propofol maintenance anaesthesia.<sup>22</sup> After 2.0 mg/kg sugammadex, recovery to a normal neuromuscular function was equivalent under propofol and sevoflurane maintenance anaesthesia. A multicentre dose-finding and safety study investigated the reversal of rocuronium-induced neuromuscular block by sugammadex at 5 min after the administration of rocuronium.<sup>23</sup> After a high dose rocuronium (1.2 mg/kg) for intubation, the patients received either placebo or sugammadex in a dose up to 16.0 mg/kg 5 minutes after the injection of rocuronium. A dose of sugammadex of 16.0 mg/kg resulted in a recovery time of less than 2 minutes compared with 122 minutes for placebo. Residual blockade or recurarization were not reported. Sugammadex caused a dose-dependent, fast and efficient reversal of profound rocuronium-induced neuromuscu-

lar block. Evaluation of safety data indicates that sugammadex was well tolerated at doses up to 16.0 mg/kg. In another study the dose-response relationship of sugammadex for the reversal of shallow rocuronium and vecuronium-induced neuromuscular block was evaluated.<sup>24</sup> Thirty nine patients received 0.6 mg/kg rocuronium and 40 received 0.1 mg/kg vecuronium. Both groups were treated with either placebo or up to 8.0 mg/kg sugammadex at reappearance of the second twitch of the train-of-four ratio. Again, a normal neuromuscular function was the primary end-point of this study. Sugammadex showed a fast and effective recovery after a rocuronium and vecuronium-induced neuromuscular block. A clear dose-response relationship was observed. Again, residual blockade or recurarization were not reported. No adverse events related to sugammadex were reported and sugammadex showed an excellent safety profile. A multicentre study evaluated the efficacy of sugammadex in reversal profound neuromuscular block induced by 1.2 mg/kg rocuronium.<sup>25</sup> Randomly at 3 or 15 minutes after the injection of rocuronium, sugammadex was administered in doses up to 16.0 mg/kg. A dose dependent time to recovery to a normal neuromuscular function was found. The reversal time was significantly decreased compared with placebo. Only one adverse event was reported possibly related to sugammadex (QT-prolongation).

An interesting study was conducted in which reversal of rocuronium-induced neuromuscular block by sugammadex was compared with the reversal of the currently used combination of cholinesterase inhibitors and muscarinic acetylcholine receptor antagonists, neostigmine-glycopyrrolate and edrophonium-atropine.<sup>26</sup> Sixty patients undergoing elective surgery with standardized general anaesthesia (desflurane-remifentanyl and rocuronium 0.6 mg/kg as first bolus and for maintenance 0.15 µg/kg) received either sugammadex 4 mg/kg (n=20), edrophonium 1 mg/kg with atropine 10 µg/kg (n=20), or neostigmine 70

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$\mu\text{g}/\text{kg}$  with glycopyrrolate  $14 \mu\text{g}/\text{kg}$  ( $n=20$ ) for the reversal of NMB at 15 minutes or longer after the last dose of rocuronium. The reversal of rocuronium-induced neuromuscular block by sugammadex was more rapid and efficient compared with neostigmine-glycopyrrolate or edrophonium-atropine. In the neostigmine and glycopyrrolate group heart rates were significantly higher at 2 and 5 minutes after the reversal than with sugammadex. The incidence of dry mouth was significantly reduced in the sugammadex group. This study showed that the reversal of rocuronium-induced NMB with sugammadex is more rapid and efficient and associated with less side-effects frequently reported after reversal with cholinesterase inhibitors.

Another study compared the efficacy and safety of sugammadex for reversal of profound rocuronium-induced ( $1.2 \text{ mg}/\text{kg}$ ) NMB with that of spontaneous recovery from succinylcholine-induced (intubating dose of  $1.0 \text{ mg}/\text{kg}$ ) NMB.<sup>27</sup> Sugammadex was administered 3 minutes after induction of profound NMB. Two groups of each 55 patients received either sugammadex or succinylcholine. Heart rate and blood pressure were similar between groups and no signs of residual or reoccurarization. Reversal of profound rocuronium-induced NMB with sugammadex was significantly faster than spontaneous recovery from succinylcholine-induced NMB. Both treatments were well tolerated. The authors concluded that in a hypothetical scenario of failed intubation following rocuronium, immediate reversal with sugammadex is feasible.<sup>27</sup>

A further study evaluated the effect of sugammadex on the individually corrected QTc interval (QTcI). Sixty-two volunteers received either a dose of  $4.0 \text{ mg}/\text{kg}$  sugammadex (therapeutic dose) or  $32 \text{ mg}/\text{kg}$  (supra-therapeutic dose), moxifloxacin (moxifloxacin is known to induce QTc prolongation)  $400 \text{ mg}/\text{kg}$  or placebo. The results showed that treatment with single doses of therapeutic and supra-therapeutic sugam-

madex were not associated with QTc prolongation. Sugammadex was safe and well tolerated.<sup>28</sup>

From recent publications it may be concluded that sugammadex is able to effectively and safely reverse rocuronium-induced NMB in healthy volunteers and in patients scheduled for elective surgery in ASA I and II class patients. However, it is extremely important to know the efficacy and safety of sugammadex in reversing rocuronium-induced NMB in more vulnerable patients groups, such as patients with renal failure, pulmonary disease, cardiac disease, pediatric patients and elderly patients.

#### *Patients with renal impairment*

An important study was performed in which the efficacy and safety of sugammadex in reversing the effect of rocuronium in patients with renal failure was investigated. Thirty patients (16 female, 14 male, 29-81 years) participated in this study. Fifteen patients had impaired renal function (creatinine clearance  $< 30 \text{ ml}/\text{min}$ ) and 15 patients had a normal renal function (creatinine clearance  $> 80 \text{ ml}/\text{min}$ ). An intubating dose of rocuronium  $0.6 \text{ mg}/\text{kg}$  was administered and neuromuscular monitoring was performed using TOF stimulation. Sugammadex was given at reappearance of T<sub>2</sub> and endpoint was a TOF ratio of 0.9. A mean (SD) renal function of 12 (5)  $\text{ml}/\text{min}$  was found in the renal impaired group and 103 (24)  $\text{ml}/\text{min}$  in controls. Sugammadex caused a rapid and complete recovery from rocuronium-induced NMB in patients with normal or impaired renal function. No signs of reoccurarization were observed in patients with renal impairment.<sup>29</sup>

#### *Patients with pulmonary disease*

Another study reported the safety and efficacy of sugammadex was evaluated in reversing a rocuronium-induced NMB in patients with pulmonary disease.<sup>30</sup> Patients who had a diagnosis or known history of pulmonary disease were scheduled for elective surgery. Rocuronium was administered as an intubating dose of  $0.6 \text{ mg}/\text{kg}$  with maintenance

dose of  $0.15 \text{ mg}/\text{kg}$ . Sugammadex in a dose of either  $2.0$  or  $4.0 \text{ mg}/\text{kg}$  was administered after the last dose of rocuronium at reappearance of T<sub>2</sub>. Neuromuscular monitoring was carried out using acceleromyography, in the train-of four and as the endpoint was considered a TOF ratio of 0.9. Seventy-seven patients were treated with either  $2.0 \text{ mg}/\text{kg}$  ( $n=39$ ) or  $4.0 \text{ mg}/\text{kg}$  ( $n=38$ ) sugammadex. Six patients reported one or more adverse events and two patients reported bronchospasm (in the  $4.0 \text{ mg}/\text{kg}$  group) and were classed as serious adverse events. In one case the patient was extubated 2.5 minutes after the reversal with sugammadex but before a TOF ratio of 0.9. The bronchospasm occurred 1 minute after extubation and lasted for 4 minutes. The other case of bronchospasm occurred 55 minutes after sugammadex administration. However, none of the reported serious adverse events were considered related to sugammadex. In both groups vital signs showed no abnormalities and no signs of reoccurarization or residual NMB were seen. Sugammadex was well tolerated and was effective for the reversal of rocuronium-induced NMB in patients with pulmonary disease.<sup>30</sup>

#### *Patients with cardiac disease*

This study reported the results of a safety and efficacy study of sugammadex for reversal of rocuronium-induced NMB in patients with a cardiac history. Patients ( $n=121$ ) planned for elective surgery received an intubating dose of rocuronium  $0.6 \text{ mg}/\text{kg}$  with maintenance doses  $0.1-0.2 \text{ mg}/\text{kg}$ . At reappearance of T<sub>2</sub> either sugammadex  $2.0$  or  $4.0 \text{ mg}/\text{kg}$  or placebo was administered. Safety assessment consisted of analysis of ECG data (QTc (Friderica)). These ECG data gave no indication of a possible prolongation effect on QTc (F). Reversal was considerably faster with sugammadex compared with placebo. The authors suggest that sugammadex is a safe and effective agent for the reversal of rocuronium-induced NMB in cardiac patients.<sup>31</sup>

### Paediatric patients

An interesting study compared the effects of sugammadex on reversal of rocuronium-induced NMB in paediatric and adult patients. Eight infants (28 days-23 months), 24 children (2-11 years), 31 adolescents (12-17 years) and 28 adults (18-65 years) were anesthetized with propofol and opioids or caudal analgesia (infants) and received rocuronium 0.6 mg/kg. The patients were treated with either sugammadex 0.5, 1.0, 2.0 or 4.0 mg/kg or placebo at reappearance of T<sub>2</sub>. Safety was assessed by recording vital signs, ECG, laboratory data and adverse events. Recovery time from this NMB decreased in a dose dependent manner in all age groups. Residual or recurarization was not observed. The authors concluded that sugammadex was effective and safe for reversal of rocuronium-induced NMB in paediatric and adult patients.<sup>32</sup>

### Elderly patients

A further study assessed the efficacy and safety of sugammadex for the reversal of rocuronium-induced NMB in adult and elderly patients. NMB was induced by an intubating dose of rocuronium 0.6 mg/kg with maintenance dose of 0.15 mg/kg. Sugammadex 2.0 mg/kg was administered after the last dose of rocuronium at reappearance of T<sub>2</sub>. Of the 150 patients treated with sugammadex, 48 were aged 18-64 years (adult group), 62 were aged 65-74 years (elderly group) and 40 were aged above 75 years (old elderly group). Recovery from rocuronium-induced NMB with sugammadex 2.0 mg/kg was slightly faster in patients aged less than 65 years. There were no signs of recurarization or residual NMB. The authors concluded that sugammadex was effective and well tolerated for the reversal of rocuronium-induced NMB in adult, elderly and old elderly patients.<sup>33</sup>

### Pharmacokinetics of sugammadex

The pharmacokinetic profile of sugammadex and rocuronium has been investigated in healthy volunteers and surgical patients.<sup>18,20,34</sup> In these

studies, sugammadex and rocuronium concentrations in plasma and urine were measured in subjects receiving either sugammadex alone, or receiving an intubating dose of rocuronium 0.6 mg/kg followed by a bolus administration of placebo or one of multiple dose of sugammadex (up to 8 mg/kg in patients and in healthy volunteers). Sugammadex showed dose-linear pharmacokinetics, a distribution volume of 18 L, an elimination half-life of 100 minutes, and plasma clearance of sugammadex of 120 ml/min, with up to 80% of the dose being excreted in urine over 24 hours.<sup>18,20,34</sup> In the pharmacokinetic studies the assay methods did not discriminate between sugammadex-rocuronium complex and free sugammadex and rocuronium because the free and bound concentrations of sugammadex cannot be measured separately.<sup>18,20,34</sup>

After encapsulation by sugammadex, rocuronium is no longer free to distribute over the body, but instead is confined to the space in which sugammadex resides. The volume of distribution of rocuronium decreases with increasing dose of sugammadex until the volume of distribution of rocuronium approaches the volume of distribution of sugammadex at higher doses. Encapsulation results in inactivation of the rocuronium molecule, changing its pharmacodynamics. In addition, there is a change in the pharmacokinetics of rocuronium, i.e. redistribution from the tissue compartment (including the neuromuscular junction) to the plasma compartment. This redistribution of rocuronium represents an important contributory factor to the efficacy of sugammadex, especially within the first few minutes following administration.<sup>18,20,34,35</sup> Encapsulation of rocuronium by sugammadex in plasma will result in a rapid decrease in free rocuronium concentration in this compartment, although the measured total plasma concentration (bound and unbound rocuronium) actually increases. This results in a concentration gradient between a relatively high level of free rocuronium in the effect compartment, i.e. the neuromuscular

junction, and a low free level in the plasma compartment. As a result, free rocuronium molecules return to the plasma compartment and are encapsulated by free sugammadex. Thus, the increase in plasma levels of rocuronium after sugammadex administration illustrates the mechanism responsible for the rapid reversal of neuromuscular blockade by sugammadex.

Another factor is the renal clearance of both free and complexed sugammadex and rocuronium. In the absence of sugammadex, rocuronium is mainly excreted in bile and faeces and only limited amounts (less than 20% of rocuronium 0.6 mg/kg) are excreted in urine.<sup>35</sup> When sugammadex is administered also, renal excretion of the sugammadex-rocuronium complex predominates as the large size of the complex prohibits extra-renal excretion. In addition, bound plasma rocuronium levels increased, and renal excretion of rocuronium was enhanced by the administration of sugammadex compared to placebo.

The main difference in the pharmacokinetic profile of sugammadex and rocuronium is that the clearance of sugammadex is approximately three times lower than that of rocuronium.<sup>34</sup> However, when assuming that the pharmacokinetic profile of the rocuronium-sugammadex complex is similar to that of sugammadex, the lower clearance of sugammadex compared with rocuronium implies that the elimination of rocuronium is retarded by the administration of sugammadex.<sup>34</sup> In studies in healthy volunteers and surgical patients in which rocuronium 0.6 mg/kg was administered, 12-22% of rocuronium was excreted in urine in the first 12 h.<sup>18,20,34</sup> Gijzenbergh and colleagues reported that only 14% of a dose of 0.6 mg/kg rocuronium was recovered in urine within 24 h in the patient group not treated with sugammadex.<sup>18</sup> In the sugammadex-treated group, the percentage of the rocuronium dose excreted in urine increased with increasing sugammadex doses, up to 39-68% at the highest dose of 8.0 mg/kg. Similarly, a study reported by Sorgenfrei et al

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showed that sugammadex increased the proportion of the rocuronium dose (0.6 mg/kg) excreted in urine from a median of 19% in the placebo group to 53% in the highest sugammadex dose group (4.0 mg/kg) within 16 h.<sup>20</sup> Thus, the administration of sugammadex at doses up to 8.0 mg/kg promotes a 2–3 fold increase in the urinary excretion of rocuronium.

## Conclusions

The results of recent studies demonstrate that sugammadex is effective for reversal of rocuronium and vecuronium-induced neuromuscular block without apparent side-effects. This is in contrast to the currently available cholinesterase inhibitors used to reverse neuromuscular

block and which are even ineffective against profound neuromuscular block and have a number of undesirable side-effects. Sugammadex-rocuronium complexes are highly hydrophilic and it has been demonstrated that sugammadex is excreted in a rapid and dose-dependent manner in urine, resulting in a complete elimination from the body.

The ability of sugammadex to reverse rocuronium and vecuronium-induced neuromuscular block may have major implications for routine anaesthetic practice. Once sugammadex becomes commercially available, anaesthesiologists will be capable of maintaining the desired depth of neuromuscular block at any time, thereby assuring optimal surgical conditions and this new promising

concept on reversal of rocuronium-induced NMB may prevent PORC and will therefore contribute in improving patient's safety.

It has been speculated that sugammadex might also be used to rapidly terminate the effects of rocuronium in the dangerous and feared 'cannot intubate, cannot ventilate'-situation, and that it could improve the suitability of rocuronium rapid sequence induction techniques.<sup>36</sup> The mechanism by which sugammadex encapsulates rocuronium and vecuronium appears to be superior to currently neuromuscular block reversal strategies in terms of speed, efficacy, incidence of residual neuromuscular block and recurarization, and side effects.

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## case report

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### IMPACT ON DAILY PRACTICE

The sublingual administration route could be of great benefit for patients who are not able to absorb oral administered ACE-inhibitors. Sublingual administration of 20 mg lisinopril once a day resulted in angiotensin II plasma levels comparable to the levels seen after a twice daily regimen of sublingual captopril and a single intravenous administration of enalaprilat. A great advantage of lisinopril is that the drug can be administered once a day, thereby not negatively influencing compliance of the drug.

### KEYWORD

Sublingual, lisinopril, captopril, angiotensin II, plasma level

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# The effect of sublingual lisinopril on angiotensin II plasma levels

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**ABSTRACT** captopril has been used sublingually in several cardiovascular diseases for many years. A disadvantage of captopril is that the drug has to be administered two or three times a day, thereby negatively influencing patient's adherence. Lisinopril possesses a longer elimination half-life and can therefore be administered once daily. This case-report describes the effect of sublingual lisinopril on angiotensin II levels in a 44-year-old woman with heart failure, who was admitted to the intensive care unit (ICU) after resection of the small intestines. Angiotensin II plasma levels were measured prior to, 1 and 3 hours after 20 mg lisinopril sublingually once daily (sid) and compared to angiotensin II plasma levels measured after a single intravenous enalaprilat and twice daily (bid) 25 mg captopril administrations. Sublingual administration of lisinopril resulted in angiotensin II plasma levels comparable to the levels seen after sublingual captopril and intravenous administration of enalaprilat.

This case-report is the first to demonstrate that sublingual administration of 20 mg lisinopril sid resulted in angiotensin II plasma levels comparable to the levels seen after sublingual captopril 20 mg bid and a single intravenous administration of enalaprilat. A great advantage of lisinopril is that the drug can be administered once a day, thereby not negatively influencing compliance of the drug.

## Introduction

Sublingual administration of drugs is an alternative when patients are not able to absorb orally administered drugs and when intravenous administration outside a controlled setting, such as the ICU, is not recommendable. Captopril has been used sublingually in hypertensive crises [1-5] and heart failure [6-9] for more than 15 years. Consequently, much experience with and knowledge of the sublingually administered drug has been gained. Recently we reported the results of angiotensin II plasma levels after sublingual captopril administration in the same patient as described in our case below [10]. However, due to its short elimination half-life of less than 3 hours, captopril has to be administered two or three times a day. Such a dosage regimen negatively influences the compliance with (or adherence to) the prescribed medication [11]. Angiotensin converting enzyme (ACE) inhibitors that can be administered once daily are therefore preferred. Lisinopril possesses a longer elimination half-life than captopril, and has the advantage over captopril that it can be administered once daily. To our knowledge, data with respect to the use of sublingual lisinopril are not available, nor has the effect on the angiotensin II levels been studied.

We measured angiotensin II levels in plasma before and after sublingual administration of lisinopril and compared these results with sublingual captopril and intravenous enalaprilat in a patient with heart failure.

## Case description

A 44-year-old woman was admitted to the ICU after resection of the small intestines. Her medical history consisted of familial adenomatous polyposis (FAP) for which in 2000 a proctocolectomy and ileal-pouch anal anastomosis were performed. Subsequent anatomic-pathologic examination showed an adenocarcinoma. In 2003, the patient presented with metastasis located in the pancreas. Initial treatment of the metastasis consisted of irinotecan and

oxaliplatin. The chemotherapy was followed by a partial pancreaticoduodenectomy according to Whipple. The same day complete resection of the small intestines was performed because of transmural ischemia. After admission to the ICU creatin kinase, troponin T and lactate dehydrogenase rose to 3817 U/l, 16 µg/l and 1987 U/l, respectively, providing evidence for ischemia of the heart, with no clear echocardiographic abnormalities. A transesophageal echocardiography showed an ejection fraction of 40%.

Due to the absence of both the large and small intestines, the patient was restricted to intravenous administration of drugs and nutrition. To minimize the number of intravenous administrations, lisinopril sublingually was started after captopril sublingually and a single intravenous enalaprilat administration. Prior to participation, informed consent was obtained from the patient.

The patient received intravenous enalaprilat 2 mg for one day. After a wash-out period of two days, captopril 25 mg bid for two consecutive days was started sublingually. This administration was followed by a second wash-out period. After two days, 20 mg lisinopril sublingually sid was started for 5 consecutive days. Lisinopril, enalaprilat and captopril were administered the same time of the day. The second dose of captopril was administered 12 hours after the first dose. Blood samples were taken prior to, 1 and 3 hours after administration of captopril (day 1 and 2), enalaprilat and lisinopril (day 1, 2, and 5). During this period the patient remained immobilised in bed, indicating constant and consistent activity, thereby limiting its influence on angiotensin II levels. Plasma samples were collected in cold EDTA-tubes, extracted and analyzed for angiotensin II levels by a competitive radioimmunoassay (Eurisa-angiotensin II kit, Euro-Diagnostica AB, Sweden). The coefficient of variation (%; n=20) of this assay method is 3.3% and 3.0% at concentrations of 15.7 and 76.7 µg/l, respectively. Cross reactivity

at 50% binding for angiotensin II and angiotensin I is 100% and <0.1%, respectively.

## Results

Baseline levels of angiotensin II did not differ for enalaprilat and captopril administration (8.1 pmol/l vs. 8.2 pmol/l, respectively). For lisinopril the baseline level (4.4 pmol/l) was discounted because the sample was not collected in a cold tube. Assuming the same angiotensin II baseline level, the effect of sublingual lisinopril on angiotensin II levels was manifest within one day of treatment (at day 1, t=1 hour 5.2 pmol/l), whereas the effect of captopril was seen after one day of treatment (at day 2, t=0 hour 5.2 pmol/l; Table 1). Angiotensin II plasma levels after sublingual administration of lisinopril were comparable to the levels found after sublingual captopril and intravenous enalaprilat administrations. Throughout the treatment period, angiotensin II levels after lisinopril administration remained consistently low.

The tablets were well tolerated when given sublingually. Side effects, such as headache, dizziness, and an itching cough, or any negative effects on taste of the sublingually administered drugs were not reported.

## Discussion

This case-report is the first to describe the use of sublingually administered lisinopril. The effect of sublingual lisinopril on angiotensin II levels was comparable with the effect seen after sublingual captopril and intravenous enalaprilat administration. Furthermore, the angiotensin II level remained consistently low during the treatment period. A great advantage of lisinopril over captopril is that it can be administered once daily. Captopril has a shorter elimination half life than lisinopril, resulting in a two or three times daily regimen. Such a regimen negatively influences the compliance with (or adherence to) the prescribed medication [11]. Non-compliance is a common problem in patients with heart failure [12] and

## case report

may lead to increased hospitalisation, morbidity, and mortality [13, 14]. Reducing the number of daily doses required, results in a higher compliance [11] and is therefore recommended for life-long treatment.

The baseline angiotensin II level of lisinopril was discounted since the blood sample was not collected in a cold EDTA-tube, and was therefore considered not reliable. Before administration of lisinopril a wash-out period of two days was used for reaching angiotensin II baseline level. Since the elimination half life of captopril is less than three hours, it is likely that the angiotensin II level had returned to baseline concentration before lisinopril administration. Furthermore, during the study period the patient remained immobilised, thereby limiting the influence of activity on the angiotensin II level.

In our case, we did not find an effect on the angiotensin II levels after the first dose of sublingual captopril. On the second day of treatment, we found a comparable effect to intravenous enalaprilat. The lack of effect after the first dose is surprising, since sublingually administered captopril has been shown to be an effective drug in emergency situations. Several studies showed a direct effect of sublingually administered captopril on the blood pressure [1-5], indicating that the rate and absorption of captopril are not

**Table 1 Time course of angiotensin II (AT-II) plasma levels**

Time after administration (h)	AT-II levels (pmol/l)					
	Enalaprilat 2 mg sid	Captopril 25 mg bid		Lisinopril 20 mg sid		
	Day 1	Day 1	Day 2	Day 1	Day 2	Day 5
T = 0	8.1	8.2	5.2	4.4*	4.4	5.0
T = 1	6.4	7.9	3.8	5.2	4.2	3.1
T = 3	3.3	9.4	3.7	4.3	4.4	4.9

\* Sample taken in EDTA-tube at room temperature

limited by the drug's profile.

In patients with normal renal and hepatic function, the dosage of intravenous enalaprilat is 1.25 mg four times a day. In our case, the dosage administered was 2 mg once daily. This regimen was chosen to minimize the number of intravenous medications administered. It is important to find a balance between the registered dosage regimen and patient's comfort, especially in patients who are not able to absorb orally administered drugs.

In this case, the angiotensin II plasma levels were only monitored up to five days after start of the lisinopril administration. To find out whether chronic use of sublingual lisinopril in patients with heart failure has a similar or distinct effect on the angiotensin II levels, more data regarding longer periods of drug administration are necessary.

## Conclusion

This case-report is the first to demonstrate that sublingual adminis-

tration of 20 mg lisinopril once daily resulted in angiotensin II plasma levels comparable to the levels seen after a twice daily regimen of sublingual captopril and a single intravenous administration of enalaprilat. A great advantage of lisinopril is that the drug can be administered once a day, thereby not negatively influencing compliance of the drug [11]. Although only one case was presented, sublingual administration of lisinopril could be of great benefit for selected patients who are not able to absorb orally administered ACE-inhibitors.

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### Possible conflict of interests

The authors state that they have no conflict of interests.

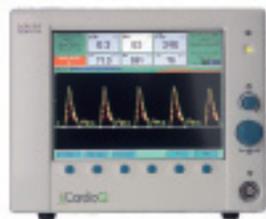
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\* Resultaat gerichte hemodynamische monitoring met coo is bewezen beter

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