

## Anaphylaxis after intravenous administration of amoxicillin/clavulanic acid in two dogs under general anesthesia

### *Anafylactische shock na intraveneuze toediening van amoxicilline-clavulaanzuur bij twee honden onder algemene anesthesie*

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## A BSTRACT

In this case series, the occurrence and successful treatment of anaphylaxis after the intravenous administration of amoxicillin/clavulanic acid are described in two dogs under general anesthesia. Within five to ten minutes after the administration of the antibiotic, a severe hypotension occurred in both dogs, accompanied by labial and periorbital swelling and erythema. Therapy consisted of counteracting the cardiovascular effects of anaphylaxis and preventing further release of inflammatory mediators. Both dogs recovered uneventfully from the drug-related anaphylaxis.

## SAMENVATTING

Deze casuïstiek handelt over het ontstaan en de succesvolle behandeling van anafylactische shock na de intraveneuze toediening van een amoxicilline/clavulaanzuurpreparaat bij twee honden onder algemene anesthesie. Binnen de vijf tot tien minuten na de toediening van het antibioticum trad bij beide honden een ernstige bloeddrukdaling op. Tevens werd een labiale en periorbitale zwelling met erytheem waargenomen. De therapie bestond uit de behandeling van de negatieve cardiovasculaire effecten van de anafylactische shock en het verhinderen van een verdere vrijstelling van ontstekingsmediatoren. Bij beide honden was de therapie succesvol.

## INTRODUCTION

Amoxicillin/clavulanic acid is an extended spectrum penicillin that is effective against most gram-positive, some gram-negative and anaerobic bacteria, and therefore has multiple therapeutic indications (Unterer et al., 2011). In Belgium, the drug is registered for use in dogs as a formulation for oral and subcutaneous administration. However, for perioperative antibiotic prophylaxis, the intravenous (IV) administration of antibiotics is usually preferred above other routes of administration, especially if there is a septic risk profile, since therapeutic plasma concentrations are reached more rapidly (Boothe, 2001). Since there is no registered amoxicillin/clavulanic acid preparation for IV administration in dogs, a preparation registered for humans can be used. However, timely administration of an antibiotic preparation registered for subcutaneous administration in dogs is a good alternative to achieve adequate plasma concentrations during elective surgery.

Like any other drug, the administration of antibiotics carries the risk of anaphylactic reactions. In

human medicine, intravenous antibiotics are responsible for most of the reported drug-related anaphylactic reactions, followed by non-steroidal anti-inflammatory drugs (NSAIDs), antineoplastic/cytotoxic drugs, immune modulators, vaccines and radiographic contrast agents (Van der Klauw et al., 1993; Lee and Shanson, 2007; Klimek et al., 2012; Ribeiro-Vaz et al., 2013). A recent human retrospective study showed that as much as 49.6% of the reported anaphylaxis cases (of a total of 333 cases) were caused by antibiotics, and that amoxicillin was involved in nearly one third of the cases (Renaudin et al., 2013). Although the veterinary literature reports on anaphylaxis caused by the same drugs as described in human medicine (Shmuel and Cortes, 2013), the authors did not find any case report on anaphylaxis following IV amoxicillin/clavulanic acid administration in dogs.

This case series presents two cases of apparent anaphylaxis after the IV administration of amoxicillin/clavulanic acid (Augmentin<sup>®</sup>P 500 mg/50 mg; GlaxoSmithKline, Italy) at a dose of 20 mg/kg during inhalation anesthesia in dogs.

## CASE PRESENTATIONS

### Case 1

A 2.5-year-old, male English bulldog weighing 29 kg was hit by a car. At admittance to the Department of Medicine and Clinical Biology of Small Animals of the Faculty of Veterinary Medicine (Ghent University), a large rectangular skin abrasion (50 x 6 cm) was present at the right lateral thorax. Additionally, a neurological diagnosis of brainstem or cervical trauma (C1-C5) was made, based on the presence of mild ataxia and a hypermetric gait on the front legs. The dog was kept in observation for the neurological symptoms, analgesic treatment and treatment of the skin abrasion, which included oral amoxicillin/clavulanic acid (Clavubactin 500 mg/125 mg; Le Vet, the Netherlands) 12.5 mg/kg q 12 h PO (from day 4 onwards, when the lesion had become necrotic). On day 6, the dog was scheduled for surgical correction of the skin wound. Pre-anesthetic evaluation and blood work revealed no abnormalities, and the dog was considered to be an 'American Society of Anesthesiologists (ASA) grade II patient' (mild systemic disease, no incapacity). A 20-gauge catheter was aseptically placed in a cephalic vein. Premedication consisted of methadone 0.2 mg/kg (Mephenon; Denolin, Belgium) IV, and the degree of sedation was considered sufficient. Fifteen minutes later, anesthesia was induced with propofol 3.5 mg/kg (Propovet; Abbott Animal Health, UK) IV. Subsequently, a 7-mm internal diameter cuffed endotracheal tube was placed, and anesthesia was further maintained with isoflurane (Isoflo; Abbott Animal Health, UK) vaporized in oxygen using a rebreathing system with a fresh gas flow of 1 L/minute. A lactated Ringer's solution (Hartmann; Baxter, Belgium) was infused IV at 10 mL/kg/hour throughout anesthesia. Following the induction of anesthesia, carprofen 2 mg/kg (Rimadyl; Pfizer Animal Health, Belgium) was administered IV. The dog was allowed to breathe spontaneously during the preparation for surgery, but was mechanically ventilated during the surgical procedure. During anesthesia, the respiratory rate, heart rate (HR), arterial oxygen saturation, systolic (SAP), diastolic (DAP) and the mean arterial (MAP) blood pressures (indirect oscillometric method, median artery, midradial region), inspired oxygen percentage (FiO<sub>2</sub>), inspired isoflurane percentage, end-tidal isoflurane percentage (FE'ISO) and end-tidal partial pressure of CO<sub>2</sub> were measured continuously (Cicero; Dräger, Germany), and recorded every 10 minutes. A three-lead electrocardiogram was attached (Datex Cardiocap; Datex-Ohmeda, Finland). The patient was positioned on a circulating hot water mattress (Gaymar TP500; Gaymar Industries Inc., USA).

During the first 20 minutes of anesthesia, all measured parameters were stable and within their respective physiological reference values. After 25 minutes into the anesthetic period (before the start of

surgery), amoxicillin/clavulanic acid 20 mg/kg was administered slowly IV. Within 5 minutes following this injection, a dramatically low SAP (60 mm Hg) was observed, together with labial and periorbital swelling and erythema. At this time point, the oscillometric blood pressure monitor was not able to display a value for DAP and MAP. The heart rate was 140 beats/minute, which was not higher than the previous measurements. Ephedrine 0.1 mg/kg (Efedrine HCl; Denolin, Belgium) was administered twice IV with a 5-minute interval to treat the hypotension, but the restoration of the normal blood pressure only lasted for a short period (5-10 minutes). At the time of the second ephedrine administration, promethazine 0.4 mg/kg (Phenergan; Haupt Pharma Livron, France) was administered intramuscularly (IM). A continuous rate infusion (CRI) of noradrenaline 0.7 µg/kg/minute (Levophed; Hospira SPA, Italy) was started. This treatment was able to keep the blood pressure within normal values continuously. The noradrenaline CRI was reduced to 0.5 µg/kg/minute after 10 minutes, further reduced to 0.3 µg/kg/minute 20 minutes later and stopped 90 minutes after the onset of the suspected anaphylactic reaction. Additionally, the FE'ISO was decreased from 1.4% to 0.9% immediately following the onset of the suspected anaphylactic event. At that time, a CRI of fentanyl (Fentanyl; Janssen Pharmaceutica, Belgium) of 5 µg/kg/hour was started and intermittent positive pressure ventilation was initiated and maintained throughout anesthesia. At the time of the discontinuation of norepinephrine CRI (90 minutes after the onset of the suspected anaphylactic shock), the facial swelling and erythema had disappeared and the normal blood pressure was maintained without further treatment during the remaining anesthetic period (another 40 minutes). The surgical resection of necrotic skin tissue and the closure of the wound were successful, and the dog's recovery was uneventful. The total anesthesia time was 160 minutes. The post-operative treatment consisted of methadone 0.2 mg/kg IV q 4 hours for 24 hours, oral amoxicillin/clavulanic acid for 5 days and oral carprofen 2 mg/kg q 12 h as well as the topical application of a silversulphadiazine ointment (Flammazine; Recipharm Parets SL, Spain) on the wound 4 times a day. The dog was discharged from the hospital 2 days after the event.

### Case 2

A 5.3-year-old, female, spayed Sheltie weighing 20 kg, was admitted for emergency surgery to the Department of Medicine and Clinical Biology of Small Animals of the Faculty of Veterinary Medicine (Ghent University) with acute bile peritonitis due to rupture of a bile bladder mucocoele. The dog had already received oral amoxicillin/clavulanic acid 12.5 mg/kg q 12 h PO for 3 weeks, and was concurrently treated for hypothyroidism with levothyroxine (Forthyron; Eurovet, Belgium) 0.01 mg/kg q 12 hours PO and for allergic dermatitis with methylprednisolon

(Moderin; Pfizer Animal Health, Belgium) 48 mg PO every 2 days. On pre-anesthetic evaluation, the dog had a HR of 176 beats/minute, a prolonged capillary refill time, tacky mucosae and weak femoral pulses. A 20-gauge catheter was placed aseptically in both cephalic veins. Pre-anesthetic blood work revealed neutrophilia ( $31.16 \cdot 10^9$ ), anemia (hematocrit: 24.5%), hypoalbuminemia (15 g/L), hypoproteinemia (total protein: 39 g/L), increased alkaline phosphatase (317 U/L), decreased urea (1.9 mmol/L) and decreased creatinine (25  $\mu$ mol/L). The dog was considered an 'ASA IV-E grade patient' (extreme systemic disease constituting a threat to life; E = emergency). Prior to anesthesia, the hypovolemic shock was stabilized with 3 IV boluses of Lactated Ringer's solution (20 mL/kg each, administered over 10 minutes) and a bolus of hydroxyethylstarch 6% 10 mL/kg (Tetraspan 6%; B Braun Melsungen AG, Germany).

Premedication consisted of methadone 0.2 mg/kg (Comfortan; Dechra, Belgium) IV. Twenty minutes later, anesthesia was induced IV with fentanyl 5  $\mu$ g/kg followed by midazolam 0.5 mg/kg (Dormicum; Roche NV, Belgium) and alfaxalone 0.25 mg/kg (Alfaxan; Vétoquinol, Belgium). Subsequently, a 7-mm internal diameter cuffed endotracheal tube was placed, and anesthesia was further maintained with isoflurane (Isoflo; Abbott Animal Health, UK) vaporized in oxygen/air ( $FiO_2 = 65\%$ ) using a rebreathing system with a fresh gas flow of 2 L/minute. Lactated Ringer's solution (Hartmann; Baxter, Belgium) was infused IV at 10 mL/kg/hour throughout anesthesia, as was fresh frozen plasma (25 mL/hour for the first half hour, followed by 50 mL/hour; total dose = 10 mL/kg). A fentanyl CRI of 5  $\mu$ g/kg/hour was infused throughout anesthesia. During anesthesia, the same vital parameters as in case 1 were monitored continuously, using similar equipment and recorded at a 10-minute interval.

Ten minutes following the induction of anesthesia, amoxicillin/clavulanic acid 20 mg/kg was administered slowly IV over 10 minutes. Within 10 minutes following the end of the administration, the arterial blood pressure dropped from 131/46 (73) [SAP/DAP (MAP)] pre-anaphylaxis to 48/17 (33), and a severe cutaneous reaction (facial and periorbital swelling with erythema) was observed. Ephedrine 0.1 mg/kg was first administered IV and was repeated together with promethazine 0.3 mg/kg IM after 5 minutes. A bolus of hydroxyethylstarch 6% of 5 mL/kg was administered 10 minutes later. Ranitidine was subsequently administered IM at a dose of 2 mg/kg. The blood pressure remained low 68/34 (49) [SAP/DAP (MAP)] and a CRI of noradrenaline of 0.2  $\mu$ g/kg/minute was started, which was increased to 0.4  $\mu$ g/kg/minute after 30 minutes. This dose restored the blood pressure to acceptable levels [the lowest measured blood pressure was 88/36 (64)]. The noradrenaline CRI was continued until the end of anesthesia (140 minutes). Skin reactions resolved during anesthesia. The total anesthesia time was 200 minutes. The recovery from anesthesia was slow and the dog was

initially hypothermic (rectal temperature: 33.6 °C). A heated air mattress (3M™Bair-Hugger™; Arizant Healthcare inc., USA) was used to increase the body temperature. The postoperative blood pressure (Doppler method, digital palmar artery) was stable (SAP between 95-130 mm Hg) without treatment. The urinary production was sufficient. The postoperative analgesia consisted of methadone 0.2 mg/kg and ketamine 1 mg/kg IV q 4 hours for the first 24 hours. Five hours postoperatively, a bolus of lidocaine 2 mg/kg (Xylocaine 2%; AstraZeneca, Belgium) was administered, followed by a CRI of lidocaine of 30  $\mu$ g/kg/minute. The antibiotics consisted of enrofloxacin (Baytril 2.5%; Bayer Animal Health, Belgium) 5 mg/kg IV q 24h and cefazoline (Cefazoline 1g; Sandoz, Austria) 20 mg/kg IV q 8h. Over the next two days however, the dog's condition worsened as a result of the primary disease and she died on the third day after surgery.

## DISCUSSION

Anaphylaxis is a severe, potentially fatal, systemic allergic reaction that occurs suddenly after contact with an allergy causing substance (Sampson et al., 2006). In 2005, the clinical characteristics for the diagnosis of anaphylaxis were delineated by a panel recruited by the National Institutes of Health and the Food Allergy and Asthma Network (Shmuel and Cortes, 2013). Anaphylaxis is considered highly likely when there is an acute onset of illness (minutes to several hours) after the administration of a possible allergen, with involvement of the skin, mucosal tissue or both in combination with a reduced blood pressure (Sampson et al., 2005; Sampson et al., 2006). The speed of the onset of the observed symptoms (within 10 minutes after the IV administration of amoxicillin/clavulanic acid) in both described cases, together with the organ distribution of the symptoms (skin and cardiovascular system) therefore strongly support the diagnosis of anaphylaxis related to the administration of amoxicillin/clavulanic acid.

Since the anaphylactic events occurred quickly after the administration of amoxicillin/clavulanic acid, this drug most likely caused the anaphylactic reactions. However, other perioperatively administered drugs, such as opioids and NSAIDs, are also commonly identified as allergens in the veterinary literature (Shmuel et al., 2013). It is therefore difficult to definitely exclude their involvement in the observed anaphylaxis. The administration of fresh frozen plasma in case 2 was started after the occurrence of anaphylaxis, and could thus not have caused the event. Besides resulting from anaphylaxis, a drop in blood pressure and a subsequent rise in HR may also result from an increased depth of anesthesia or hypovolemia. However, no signs of increased anesthetic depth were present at the time of the anaphylactic events. The pre-existing hypovolemia in case 2 was corrected preoperatively, and the initial blood

pressure measurements during anesthesia were within reference ranges. Additionally, the observed facial swelling and erythema are typical symptoms associated with histamine release during anaphylaxis, and cannot be explained as a consequence of anesthesia (Girard and Leece, 2010).

Anaphylaxis can be classified as immunologic and nonimmunologic anaphylaxis (Simons et al. 2011). Immunologic anaphylaxis is subdivided in immunologic immunoglobulin E (IgE)-mediated and non-IgE mediated anaphylaxis. The former involves a true immune-mediated response at which during the first exposure to a drug, IgE antibodies are produced, which bind to specific receptors on mast cells and basophil membranes. Following the second exposure to the same drug or when there is cross-reactivity at IgE-receptors with other drugs or chemicals (at the first exposure to a drug), the binding of the antigen to these receptors results in receptor activation and ultimately results in histamine, prostaglandin and leukotrienes release (Armitage-Chan, 2010; Simons et al., 2011). These mediators evoke a variety of symptoms associated with anaphylaxis (edema, erythema, pruritus of the skin; hypotension, tachycardia, syncope, cardiovascular collapse, increased vessel permeability; bronchoconstriction; diarrhea, vomiting) (Armitage-Chan, 2010; Girard and Leece, 2010; Ribeiro-Vaz et al., 2013). Beta-lactam antibiotics, such as amoxicillin/clavulanic acid, commonly cause immunologic IgE-mediated anaphylaxis (Antunez et al., 2006; Simons et al., 2011; Ansari et al., 2012). The immunologic non-IgE mediated anaphylaxis is caused by immune aggregates, complement or coagulation system activation and autoimmune mechanisms (Simons et al., 2011). In nonimmunologic anaphylactic reactions (also classified as anaphylactoid reactions), the observed symptoms are a result of the direct release of mast cell and basophil mediators, and may thus appear at the first exposure to a drug (Johansson et al., 2004; Descotes et al., 2007; Armitage-Chan, 2010; Girard and Leece, 2010). Chemotherapeutic drugs, contrast agents, vancomycin, NSAIDs, local anesthetics and opiates commonly cause nonimmunologic drug reactions (Farnam et al., 2012).

A true differentiation between immunologic IgE-mediated and the other forms of anaphylaxis is only possible following *in vitro* specific IgE tests, an oral challenge or bronchoprovocation test or skin testing for selected substances (Farnam et al., 2012). Since none of these tests were performed in the present cases, it is impossible to definitely classify the observed adverse reactions. However, an IgE-mediated anaphylaxis seems most likely, since beta-lactam antibiotics are known to cause IgE-mediated anaphylaxis, and prior administration of the antibiotic might have resulted in IgE-antibody production (both dogs received oral amoxicillin/clavulanic acid before anesthesia). Non-IgE mediated anaphylaxis due to cross-reactivity of another chemical comprised in the chemical prepara-

tion of the amoxicillin/clavulanic acid preparation is impossible, since the used preparation is free of any excipient. However, true IgE mediated anaphylaxis can be suspected to result in the reoccurrence of anaphylaxis when the inflicting drug is readministered, regardless of the route of administration. In case 1, the amoxicillin/clavulanic acid treatment was continued PO in the postoperative period; however, without reoccurrence of anaphylaxis. Park et al. (1992) stated that the route of administration of antigens is important in determining the type of generated allergic response, with the parenteral route being most sensitizing for the development of IgE-mediated anaphylaxis. Since intravenous infusion of an allergen is associated with the risk of more severe reactions, the risk of fatal anaphylaxis is also greater in patients receiving parenteral amoxicillin or penicillin than in patients receiving oral administration (Park and Kitteringham, 1992, Brazilian Association of Allergy and Immunopathology and Brazilian Society of Anesthesiology, 2013; Renaudin et al., 2013; Shmuel et al., 2013). Therefore, it might be that the antigen challenge after oral administration in the postoperative period was not able to elicit reactions in the dog of case 1. At the Department of Medicine and Clinical Biology of Small Animals of the Faculty of Veterinary Medicine (UGent) and at other facilities, the authors know of several, less well-documented cases of dogs suffering from an allergic reaction resulting from the IV administration of the same amoxicillin/clavulanic acid preparation, in both awake and anesthetized dogs. However, the authors have never observed any anaphylactic reaction during oral treatment. Regardless of these findings, the authors believe that the continuation of amoxicillin/clavulanic acid and other beta-lactam antibiotics by any route of administration after suspected anaphylaxis related to the administration of these drugs should be avoided.

The treatment of anaphylaxis is a medical emergency and is based on three phases. The first phase focuses on the withdrawal of the patient from the causative allergen, whenever possible. In the second phase, the clinical effects of anaphylaxis are counteracted. These include airway management, oxygen supplementation, fluid therapy, discontinuation of anesthesia and immediate medical therapy (Girard and Leece, 2010). Epinephrine is considered the drug of choice in anaphylactic shock, and can best be administered in dogs as an IV CRI of 0.05  $\mu\text{g}/\text{kg}/\text{minute}$  (Mink et al., 2004; Sampson et al., 2006; Girard and Leece, 2010; Simons and Simons, 2010). Epinephrine activates both  $\alpha$  and  $\beta$ -receptors, resulting in increased systemic vascular resistance and a subsequent increase in blood pressure ( $\alpha_1$ -receptor activation), an increase in cardiac output, myocardial oxygen consumption, coronary artery dilatation ( $\beta_1$ -receptor stimulation), bronchodilation, decreased peripheral vascular resistance, decreased release of inflammatory mediators from mast cells and basophils and relief of urticaria ( $\beta_2$ -receptor stimulation) (Peck et al., 2008a; Simons

et al., 2011). However, the different effects are dose-dependent, with  $\beta$ -effects predominating at low doses and  $\alpha$ -effects predominating at high doses (Peck et al., 2008a; Shmuel and Cortes, 2013). The third phase of anaphylaxis therapy consists of the prevention of further release of anaphylactic mediators by means of ancillary treatments, and includes the use of glucocorticoids, antihistaminics (ranitidine/cimetidine) and bronchodilators (Girard and Leece, 2010; Shmuel and Cortes, 2013). These additional treatments should be patient-based and tailored to the type and severity of the clinical signs.

The animals in the present cases were treated by different anesthetists. Anaphylaxis occurred during anesthesia. Therefore, the treatment was somewhat different from the guidelines above, and was approached as an anesthesia complication with hypotension as primary problem. Anesthesia might exacerbate the hypotension induced by anaphylaxis. Ansari et al. (2012) therefore highlight the importance of the administration of antibiotics and non-anesthetic agents 30 minutes before the induction of anesthesia rather than along with anesthetic agents, to prevent the onset of anaphylaxis during anesthesia. Strict adherence to this protocol might help avoid morbidity. In the described cases, the animals' vital parameters had already been well-monitored at the time of the onset of anaphylaxis, fluid therapy had already been installed, there was a patent secured airway and oxygen delivery was ongoing. In case 1, ideally, anesthesia should have been discontinued, whereas in case 2, this was no option since surgery was life-saving. In case 1, IV ephedrine and norepinephrine and IM promethazine were selected as medication treatment. In case 2, a combination of IV plasma-expander administration, IV ephedrine and norepinephrine, IM promethazine and IV ranitidine was chosen. Ephedrine and norepinephrine were used as an alternative to epinephrine in the present cases. Ephedrine is an "inoconstrictor" ( $\beta_1$ - and  $\alpha$ -receptor effect) that increases the cardiac output, heart rate, blood pressure, coronary blood flow and myocardial oxygen consumption. It also causes bronchodilation (Peck et al., 2008a). Systemically infused norepinephrine causes vasoconstriction and a subsequent rise in blood pressure, but causes cardiac output to fall (Peck et al., 2008a). Promethazine is a phenothiazine with strong antihistamine effects and significant anticholinergic properties (Peck et al., 2008b). The blood pressure was successfully restored in both patients, and the skin reactions were transient following the respective treatments. The dogs recovered from the anaphylactic episode within 90 and 140 minutes, respectively for cases 1 and 2.

In conclusion, the intravenous administration of a specific amoxicillin/clavulanic acid preparation caused anaphylaxis in two dogs during anesthesia. Therapy focusing on the counteraction of the cardiovascular effects of anaphylaxis and the prevention of further release of anaphylactic mediators was successful in reversing the anaphylactic reactions.

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## Uit het verleden

### DE LINTWORM

“Zijn lichaam is plat als een lint, tot vijfzes meters lang, zijne leden gelidwijze of articulatum, zoo de Latijnen zeggen, afgedeeld. Ieder lid – en daar zijn er machtig vele – is bekwaam om op zijn eigen eieren voort te brengen, al zate er maar een lintworm gansch alleen in het lijf. Die eieren laat de worm uit de menige eiranden en door den eierweg, waarvan ieder lid voorzien is, uitewaarts gaan. Het hoofd van den lintworm staat boven op het smalste ende van zijn lijf. Het is vierkante en voorzien op de vier hoeken van vier zuigers, gelijk aan de zuigers waarmee de vliegenpooten zich aan de ruiten vast houden. De mondopening staat boven op den kop en is omringd door een wielken alderfijnste klouwkens, die overhands open- en toe gaan. Met dien mond en die klouwen weet de lintworm zijnen nooddrift te zichten (voedsel te zeven) en te zuigen uit de verteerde menschen spijs, terwijl zij staat om levend bloed te veranderen. De lintworm en verteert niet noch laat eenig overblijfsel van spijs uitewaarts zijn lichaam gaan. De mensch bij wien hij wonachtig is, doet dat al voor hem. Al dat de lintworm doet is eten, leven, eieren voort brengen, en 't wordt bevestigd van hen die 't weten dat een lintworm tot 10 miljoen eieren kan in hebben en meer, na de lengde zijns lijfs.”

Uit: Guido Gezelle's “*Uitstap in de Warande*” (1865-1870 en 1882, 6de uitgave 1927, De Meester, Wetteren, 1927).

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