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DIAGNOSTIC ADVANCE

Clinical pharmacology of intravenous paracetamol in perinatal medicine

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Abstract

Clinical pharmacology aims to predict drug-related effects based on compound and population specific pharmacokinetics (PK, concentration-time), and pharmacodynamics (PD, concentration-effect). Consequently, dosing needs to be based on the physiological characteristics of the individual patient. Pregnancy and early infancy hereby warrant focused assessment. The specific characteristics of both subpopulations will be illustrated based on observations on intravenous (*iv*) paracetamol PK and PD collected in these specific populations. At delivery, there is a significant higher paracetamol clearance (+ 45%, L/h) when compared to non-pregnant observations. This higher clearance is in part explained by a proportional increase in oxidative metabolite production, but mainly an increase in glucuronidation. When focusing on PD, an association between maternal paracetamol exposure and atopy in infancy and fetal gastroshizis has been reported. In early infancy, paracetamol clearance is significantly lower and mainly depends on size (weight 0.75), while also the distribution volume is higher (L/kg). Reports on hepatic tolerance, haemodynamic stability and impact of body temperature have been published while the concentration effect profile for analgesia seems to be similar between neonates and children. Similar to maternal exposure, there are reports on the association with atopy. Studies on the use of paracetamol to close the patent ductus arteriosus are ongoing. At least, these observations provide evidence on the need to study commonly administered anesthetics in such specific subpopulations with specific focus on both population specific PK and PD to further improve patient tailored pharmacotherapy.

Key words: Pregnancy; Newborn; Intravenous paracetamol; Pharmacokinetics

Core tip: Although urgently needed to further improve patient tailored pharmacotherapy, data on the clinical pharmacology in pregnant women and young infants are limited, even for commonly used drugs like paracetamol. We summarize the available observations on both pharmacokinetics and pharmacodynamics of intravenous paracetamol in pregnant women and early infancy to illustrate the relevance of subpopulation specific observations. This includes differences in metabolic routes of elimination, in (side) effects (*e.g.*, analgesia, hypotension, atopy) and in potential indications (patent ductus arteriosus).

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INTRODUCTION

Clinical pharmacology in special populations

The general pharmacokinetic principles of disposition

and elimination of drugs apply, irrespective of population specific characteristics[1-5]. However, pregnancy and early infancy warrant a tailored approach. This is because important alterations in physiology affect drug disposition up to clinical relevance. Pregnancy results in extensive alterations in pharmacokinetics (PK, concentration-time profile) with a subsequent extensive inter-individual variability in drug response[6-8]. In general, renal elimination capacity is increased throughout pregnancy (*i.e.*, higher glomerular filtration rate, higher active tubular transport). Similar, the basal metabolic activity is also increased. This commonly results in higher drug metabolism (phase I and phase II processes), although these changes are in part also iso-enzyme specific. This, although rarely, even may result in reduced enzymatic activity (CYP1A2 and CYP2C19) during pregnancy[6,8]. Finally, changes in body weight or binding capacity (protein changes, pH) likely will affect the volume of distribution. Similarly, duration of pregnancy, co-morbidity (*e.g.*, pre-eclampsia) or labor itself may further affect variability in drug disposition[6,8].

Early infancy is another very specific population. When we consider the physiological changes and the subsequent between individual variability in characteristics, we need to take into account that maturational changes are most prominent in infancy[7,9]. Consequently, drug disposition in early infancy differs substantially from children or adults as a result of these physiology-related maturation in absorption, distribution and subsequent elimination, either through metabolic elimination or through primary renal elimination (ADME, PK)[7,9]. In general, neonates have an overall low clearance capacity. Between subject variability can be explained by covariates such as size, weight organ function, co-administration of drugs, genetic polymorphisms, growth restriction or disease characteristics[9]. Consequently, focused studies in peripartum and in early infancy to unveil clinical relevant covariates are needed[8,9]. This is even true for a commonly administered compound like paracetamol.

Paracetamol

Paracetamol, *N*-acetyl-*P*-aminophenol (acetaminophen), is a readily available antipyretic and analgesic agent. It is the most often prescribed drug for treatment of mild to moderate pain or fever in infants, including neonates and can be administered by oral, rectal but also by intravenous route[1-5]. In the therapeutic concentration range, paracetamol is metabolized by the liver to paracetamol-glucuronide (47%-62%) and paracetamol-sulphate (25%-36%) as main metabolites, subsequently eliminated by renal route. Only 1%-4% is excreted unchanged in urine, and about 8%-10% of paracetamol is oxidized to 3-hydroxy-paracetamol and the (hepatic) toxic metabolite *N*-acetyl-*P*-benzoquinone-imine[3-5].

Paracetamol is perceived to have a good efficacy-to-safety ratio as analgesic in a wide range of patient populations[10-15]. However, since paracetamol is one of the most commonly used drugs to treat pain or fever, knowledge on the covariates of paracetamol disposition remains crucial to avoid toxicity through unanticipated variability[16-20]. In addition to oral and rectal formulations, several intravenous (*iv*) formulations became available more recently[21-25]. Such a formulation enables the administration of paracetamol when the enteral route cannot (yet) be used and should improve the predictability by the reduction in variability related to absorption[26-29].

Clinical pharmacology aims to predict drug-related effects based on drug, population and patient specific PK, concentration-time, and pharmacodynamics (PD, concentration-effect): drug dosing needs to be based on the physiological characteristics of the individual patient[8,9]. As mentioned earlier, this necessitates focused studies in specific populations, including peripartum and early infancy.

Consequently, we aim to summarize our studies on aspects of PK and PD of intravenous paracetamol either at delivery and in early infancy. For both subpopulations, this will be combined with a topical review on the clinical pharmacology of paracetamol in these patients.

CLINICAL PHARMACOLOGY OF PARACETAMOL AT DELIVERY AND IN POSTPARTUM

Despite pregnancy and peripartum related changes in PK and PD and the clinical relevance to have such data, most of the drugs administered by anaesthetists have not been extensively evaluated in this specific population. This is also true for commonly administered analgesics like *iv* paracetamol.

Paracetamol PK and metabolism

Following study registration (EudraCT 2010-020164-37) and approval by the Ethics Committee of the University Hospitals Leuven, women who were scheduled to undergo a (semi) elective Caesarean delivery were recruited. The administration of *iv* paracetamol started with a loading dose of 2 g over 15 min shortly after delivery of the newborn. Blood samples from a dedicated peripheral *iv* catheter were collected 1, 2, 4 and 6 h after loading dose administration. These samples were centrifuged and plasma was stored at -20 ℃ until high performance liquid chromatography analysis was performed. Using this approach, 36 paracetamol-time profiles following delivery were available for PK analysis[14,15].

These data were compared to data either published by Gregoire *et al*[30] in 14 women, and 23 additional PK profiles collected in young female volunteers. As illustrated in Figure 1, there is a significant increase in paracetamol clearance (L/h) in peripartum when compared to non-pregnant PK profiles (median clearance 19.6 compared to 13.3 L/h, + 45%)[11,14,21,22]. Table 1 provides a selective overview on paracetamol clearance estimates reported

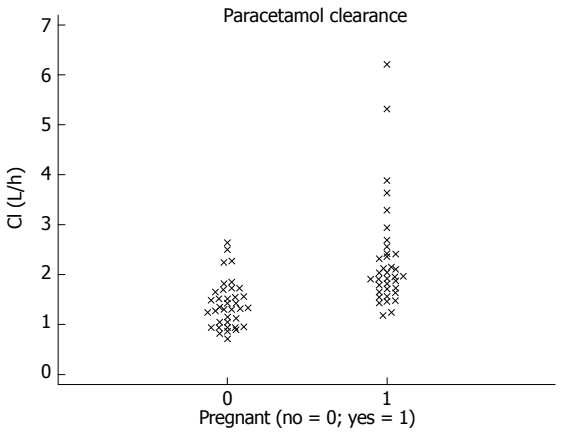

Figure 1 Individual clearance paracetamol estimates in young women at delivery compared to similar individual paracetamol clearance estimates in non-pregnant women.

in different cohorts of adults, including healthy volunteers[30,31]. In essence, this overview suggests that there are additional covariates of paracetamol clearance in adults, including disease severity, age, gender and pregnancy.

More recently and using a more sophisticated population PK modeling approach, we confirmed this a substantially higher paracetamol clearance in women at delivery compared to a subset of the same women 12 wk postpartum[6,14]. More importantly, we were able to document that this increase in total paracetamol clearance at delivery is due to a disproportional increase in glucuronidation clearance and a proportional increase in clearance of unchanged paracetamol and in oxidation clearance without any changes in the absolute sulphation clearance, resulting in a proportional decrease. These pharmacokinetic observations at delivery and in postpartum are of pharmacodynamic (analgesia, toxicity) relevance.

The link between paracetamol plasma concentration and the level of analgesia has not yet been fully described, but McNicol *et al*[18] recently reported on single dose *iv* paracetamol or propacetamol for prevention or treatment of postoperative pain based on a systematic review. Paracetamol (*iv,* 1 g) results in about 4 h of effective (pain relief, opioid sparing) analgesia with a subsequent decrease in effectiveness. Based on the paracetamol disposition (increased clearance) observed at delivery, it might be considered to decrease the time interval between consecutive paracetamol doses (at present guidelines q6h) or increase the dose (at present 1 g) in the immediate postpartum to mimic the time-concentration profile aimed for in the non-pregnant adult. However, such an approach will also results in higher oxidative metabolism (hepatotoxity) during pregnancy and is not without risk, and may explain the specific issues (gastroshizis, atopy of infancy) discussed below[32-35].

Specific pregnancy related issues as reported in literature

Epidemiological data suggest a link between perinatal paracetamol exposure and the risk to develop asthma[32,33]. This included maternal consumption of acetaminophen during pregnancy. To further illustrate this, the Avon Longitudinal Study explored the impact of both nuclear erythroid 2 p45-related factor 2 polymorphism and glutathione S-transferase (GST, M1, T1, and P1) polymorphisms in the mothers and their infants to search for genotype-phenotype concordances[32]. It was hereby documented that the antioxidant genotype of the infant did not modify associations between infant acetaminophen use and asthma phenotypes. In contrast, the increased risk of asthma and wheezing associated with late gestation acetaminophen exposure in the presence of maternal GSTM1 was further enhanced when GSTM1 was also present in the infant. Consequently, it seems that maternal antioxidant gene polymorphisms modify the relation between prenatal acetaminophen exposure and childhood asthma, strengthening evidence for a causal, polymorphisms related association[32,33]. This fits quite well with the pregnancy related differences in metabolic routes of paracetamol elimination during pregnancy since associated with higher formation of oxidative metabolites[14,32,33].

A similar illustration, but looking for genotype/phenotype concordance following maternal acetaminophen exposure and fetal gastroshizis has been elaborated by Leeder *et al*[34,35]. The author hereby also stressed that besides the maternal compartment, placental transfer and metabolism, fetal drug disposition and the developmental context also contribute to the fetal concentration/time and concentration/effect profile[34,35].

PARACETAMOL IN EARLY INFANCY

Paracetamol is also commonly prescribed to treat moderate pain in neonates and infants. Similar to other populations, an *iv* formulation may reduce variability related to absorption, and can be considered when enteral routes are not available[36]. Aspects of PK and PD of *iv* paracetamol in (pre)term neonates were collected and reported in literature[37-39]. The PK observations were recently pooled[40].

Based on this pooled population pharmacokinetic analysis in 943 paracetamol observations from 158 neonates, pharmacokinetic estimates (between-subject variability, %) were central distribution volume 51.9 L/70 kg (21.6%), peripheral distribution volume 22.7 L/70 kg and clearance 5 L/h per seventy kilogram (40%)[40]. Covariates predicted about 61% of the paracetamol clearance variability. Weight was the most important covariate of clearance, with only a very minimal additional contribution of postmenstrual age (2.2%)[40]. We hereby mainly confirmed earlier clearance estimates in a further extended cohort of (pre)term neonates[25,36].

Paracetamol clearance, described using allometric scaling was one third of the mature value reported in adults (16.2 L/h per seventy kilogram)[40]. Clearance maturation is slow before 40 wk PMA and matures rapidly

Table 1 Median paracetamol clearance estimates as reported in different cohorts of adults

Ref.	Dose	Adults	Paracetamol (L/h)
Owens *et al*[11]	1 g, repeated q6h	20 patients, major abdominal surgery	
		Day 1 of surgery	10.8
		Day 2 or 3 after surgery	16.65
Kulo *et al*[14]	2 g *iv*, followed by 1g, q6h	Caesarean delivery, 39 women	21.1
	2 g *iv*, single dose	8/39, paired analysis, 18 wk postpartum	11.7
Liukas *et al*[21]	1 g, single dose	40 patients, different age cohort, orthopedic surgery	
		20-40 years, median weight 81 kg	22.3
		60-70 years, median weight 83 kg	20.9
		70-80 years, median weight 82 kg	16.2
		80-90 years, median weight 68 kg	13.5
de Maat *et al*[22]	1 g *iv*, repeated dose	38 medium and intensive care unit adult patients	23.65
		26/38, medium care	20.84
		12/38, intensive care	39.78
Gregoire *et al*[30]	2 g *iv*, followed by 1g, q6h	26 healthy male and female volunteers	15.9
Depré *et al*[31]	0.5 g *iv*, single dose	12 healthy male volunteers	20.04

afterwards with a maturation half-time of 52 wk PMA to reach 90% of adult rates at one year of life (equal to 92 wk PMA). Moreover, when compared to other pediatric populations, the distribution volume is higher in neonates. The increased volume of distribution in neonates supports the use of a larger initial dose (loading dose) of *iv* paracetamol in neonates if one aims to attain a given threshold paracetamol concentration sooner since a higher distribution volume results in a proportionally lower peak concentration[7].

The combined observations of clearance and distribution volume result in the advice to consider a loading dose (20 mg/kg) in neonates, followed by 5, 7.5 or 10 mg/kg per six hours in extreme preterm, preterm and term cases respectively. Figure 2 provides the predicted concentration-time profile for a 36 wk postmenstrual age individual patient based on a loading dose of 20 mg/kg, followed by 10 mg/6 h[40].

Although these dosing suggestions are higher when compared to the registered dosing, the combined loading dose + maintenance (20 mg/kg, followed by 20-40 mg/kg per twenty four-hours) has been evaluated on different pharmacodynamics aspects, including both pain reduction as well as safety (hepatotoxicity, haemodynamics and body temperature)[7,10,37-39].

There were no signs of hepatic intolerance during and following repeated administration of intravenous paracetamol[39]. In addition and as part of the PARA-NEO study (www.clinicaltrials.gov, NCT00969176), we reported on the hemodynamics following *iv* paracetamol (loading dose, 20 mg/kg) administration[38]. In contrast to the negative hemodynamic effects in adult intensive care unit patients, there were no hemodynamic alterations in neonates[22,38]. Similarly, neonates remained normothermic, while temperature reduction - most pronounced within the first 2 h after administration - was observed in neonates with fever[37].

More recently, we also reported on the paracetamol concentration-effect relation in neonates, based on prospective collection in 19/60 neonates included in the PARA-NEO study received monotherapy with *iv* paracetamol to treat mild to moderate pain (*e.g.*, alprostadil administration, delivery related trauma)[10]. Using repeated measures ANOVA, there was a trend ($P = 0.02$) for lower pain scores within 30 min after administration, with a slight increase in pain scores from 5 to 6 h (Figure 3)[10]. Further analysis hereby suggests a similar paracetamol effect compartment concentration in neonates compared to children.

Specific issues reported in literature

In addition to the above mentioned aspects of clinical pharmacology of paracetamol in early infancy, epidemiological data also suggest a link between paracetamol exposure in early infancy and the risk to develop asthma similar to the link between maternal exposure and atopy in early infancy[32,33]. From a safety aspect, we would like to point to the dosage errors (10 fold error) reported following the introduction of the *iv* paracetamol formulation in neonatal intensive care unit, with serious adverse events in individual cases[41]. These errors re-illustrate the risks associated with the introduction of a new compound in this specific population.

Finally, standard pharmacologic closure of the patent ductus arteriosus currently involves the administration of 1 of 2 cyclooxygenase inhibitors: either indomethacin or ibuprofen. However, both of these drugs can be associated with potentially significant adverse effects. There have been a limited number of case reports describing the association of paracetamol exposure and closure of a patent ductus arteriosus[42,43]. At present, there are some study protocols registered who will focus on this research question in preterm neonates (< 1500 g). Until such data become available, we consider this a hypothesis in the need for validation before efficacy/safety comparative trials can be considered.

GENERAL DISCUSSION

Clinical pharmacology aims to predict PK and PD to improve the effect/side-effect balance in every individual

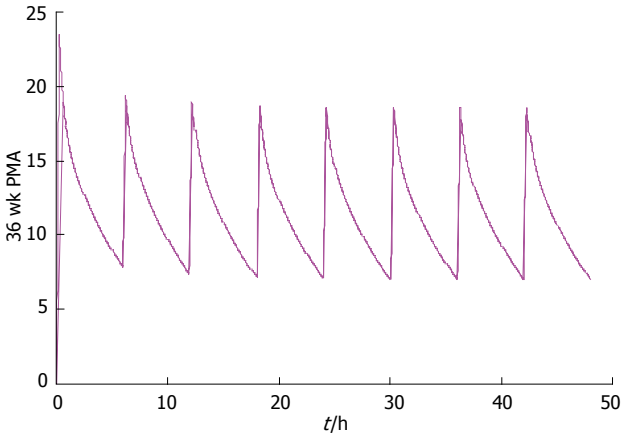

Figure 2 Concentration-time profile estimated based on the pooled pharmacokinetic study in neonates. The profile estimates are based on an initial loading dose (20 mg/kg) of *iv* paracetamol, followed by 10 mg/kg q6h in a newborn of 36 wk postmenstrual age[40].

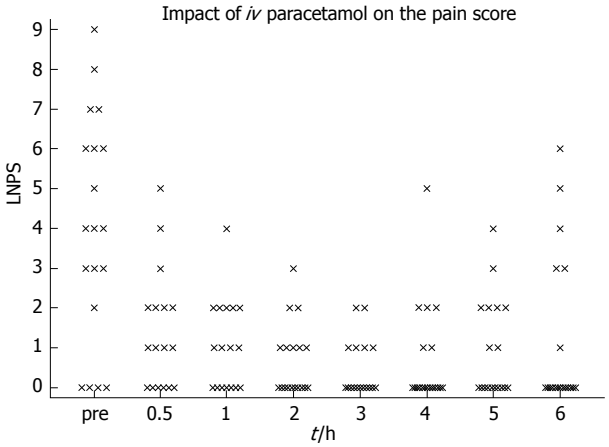

Figure 3 Individual pain scores (Leuven Neonatal Pain Score, range 0-14) as collected following *iv* paracetamol (20 mg/kg) administration. Only observations in 19/60 treated with *iv* paracetamol (monotherapy) while included in the PARANEO study were reported[10].

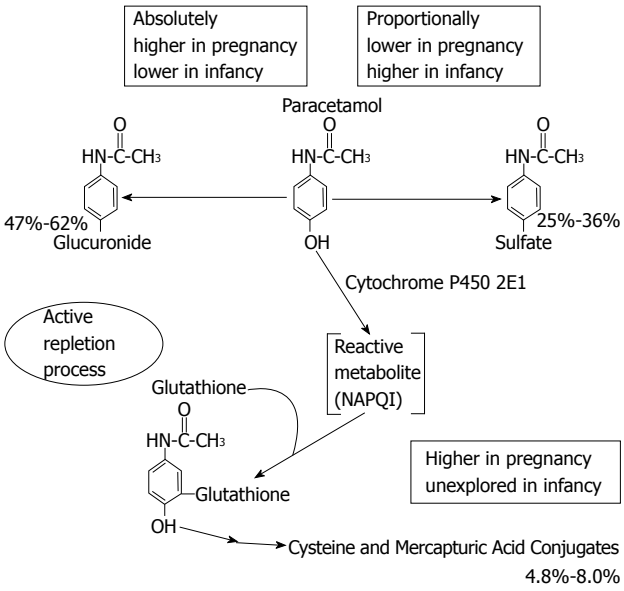

Figure 4 Paracetamol metabolism in the human, hereby indicating the changes in paracetamol drug metabolism at delivery and in early infancy.

patient. Extensive physiological alterations in pregnancy and postpartum or infancy can lead to clinically relevant changes in drug disposition and subsequent effects. This relates to the metabolic route, the pharmacokinetics (distribution volume and clearance), and the subsequent level of analgesia.

The available data reported on drug disposition in the pregnant and non-pregnant state indicate that these pharmacokinetic differences might be of pharmacodynamic relevance. Therefore, we aimed to perform additional paired PK studies in earlier and later than 3 mo postpartum stages to fully elucidate the way how pregnancy induced paracetamol disposition changes return to pre-pregnancy values[6,14]. We hereby were able to describe that the higher paracetamol clearance ad delivery is mainly due to higher glucuronidation and oxidation. In contrast, in neonates, the glucuronidation capacity is still limited, resulting in proportional higher sulphation and primary renal clearance while the contribution of oxidative metabolites to overall paracetamol clearance remains to be explored (Figure 4)[1,6,7,14].

Analgesia of paracetamol is mediated through inhibition of prostaglandins synthesis in the central nervous system (cyclo-oxygenase Ⅲ and Ⅱb). Analgesic effects also involve inhibitory action at the level of spinal nitric oxide and serotonergic pathways[1-5]. Paracetamol is believed to be an effective antipyretic at plasma concentrations between 10 and 20 mg/L and these concentrations have also been suggested to provide analgesia[1-5]. To result in effective analgesia, this means that the distribution volume needs to be considered to attain a sufficient plasma concentration at the initiation of treatment.

At delivery, the distribution volume (L) is proportionally higher due to the higher body weight at delivery, without additional relative (L/kg) changes. As mentioned earlier, the relation between plasma paracetamol concentration and the level of analgesia has not yet been fully described. Intravenous paracetamol (1 g) provides around 4 h of effective (pain relief, opioid sparing) analgesia with a subsequent decrease in effectiveness to 6 h[18]. Similarly, an intraoperative loading dose of two grams compared to one gram following minor hand or third molar surgery respectively provided better analgesia (VAS score) in the first 24 h after the intervention[44]. The higher distribution volume at delivery supports the use of a loading dose of 2 g instead of the recommended 1 g of *iv* paracetamol at delivery in the absence of contra-indications. This should be followed by 1 g *iv* paracetamol q6h to maintain these concentrations within this analgesic range while avoiding both accumulation and overproduction of oxidative metabolites[6,14].

Adequate management of pain is also in neonates a major issue, not only from an ethical perspective, but also to improve short and long term outcome[1,10]. Effective treatment of pain in this population is still in part ham-

pered due to the limited volume of data on the PK and PD of analgesics prescribed. To a certain extent, this is even true for paracetamol.

Based on their body composition, the distribution volume for paracetamol is proportionally (L/kg) higher in early infancy when compared to children or adults[40]. Similar to the rationale to use a loading dose at delivery, this pharmacokinetic variable supports the use of a loading dose (20 mg/kg). Although only based on a very limited number of observations, we recently were able to document that this loading dose approach does result in effective pain reduction up to 6 h[10]. Based on the lower clearance in early infancy, this loading dose should be followed by a maintenance dose of either 20-40 mg/kg per twenty-four hours, divided to result in intermittent administration hereby using a 6-12 h time interval[7,40].

Obviously, further studies on the pharmacodynamics of paracetamol in early infancy are urgently needed similar to the recent work of Capici *et al*[27] on the pharmacodynamics of *iv* paracetamol in children following adeno-tonsillectomy. These authors compared the time until rescue medication after adeno-tonsillectomy in children was needed after paracetamol administration. They hereby were able to document that a 6 h interval of intravenous administration (20 mg/kg) should not be exceeded. The time until rescue medication was needed was shorter after intravenous administration (6 h) compared to rectal (40 mg/kg) administration (10 h), potentially in part reflecting the slower and more variable absorption after rectal administration. Since the time until rescue medication was the main outcome variable of this study, no final conclusions on the safety/effectiveness balance during repeated rectal or intravenous administration of paracetamol can be drawn based on this study. Such studies should result in safer and more effective prescription and use of drugs in early infancy. This even is true for frequently administered drugs like paracetamol since still important issues on its use remain to be unveiled.

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CASE REPORT

Anesthetic management of patient with hypertrophic cardiomyopathy and automatic implantable cardioverter defibrillator with a hand fracture

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Abstract

A 26-year-old male with a history of hypertrophic cardiomyopathy (HCM) and ventricular arrhythmias s/p automatic implantable cardioverter defibrillator (AICD) placement presented for open reduction and internal fixation of an open third metacarpal fracture and extensor tendon repair. He underwent successful surgery after placement of an ultrasound-guided infraclavicular brachial plexus block with ropivacaine 0.5% as the main anesthetic. This case report discusses the anesthetic management of patients with HCM and AICD, different approaches available for brachial plexus blockade, and potential complications of anesthesia and surgery in this group of patients.

Key words: Hypertrophic cardiomyopathy; Automatic implantable cardioverter defibrillator; Brachial plexus block; Hand fracture; Ropivacaine

Core tip: The anesthetic management of patients with hypertrophic cardiomyopathy (HCM) and automatic implantable cardioverter defibrillator (AICD) can be very challenging. We present a case of a 26-year-old male who presented for open reduction and internal fixation of an open right hand fracture. He underwent successful surgery after placement of an ultrasound-guided infraclavicular brachial plexus block with ropivacaine 0.5% as the main anesthetic.

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INTRODUCTION

The anesthetic management of patients with hypertrophic cardiomyopathy (HCM) and automatic implantable cardioverter defibrillator (AICD) can be very challenging. We present a case of a 26-year-old male who presented for open reduction and internal fixation (ORIF) of an open right hand fracture. We discuss anesthetic implications of patients with HCM and AICD, different approaches to brachial plexus blockade, and potential risks and complications pertinent to this group of patients.

CASE REPORT

A 26-year-old Caucasian male, 70 inches tall and weighing 105 kg, presented for incision and drainage, ORIF of an open right third metacarpal fracture, and extensor tendon repair after injuring his hand at home while fixing his garage door. He had a history of hypertrophic cardiomyopathy and ventricular arrhythmias s/p insertion of an automatic implantable cardioverter defibrillator two years ago. His vital signs were a blood pressure of 99/50 mmHg, heart rate of 50, respirations of 16 per minute, and oxygen saturation of 99% on room air. Electrocar-

diogram showed sinus bradycardia (HR 54) with sinus arrhythmia and occasional premature ventricular contractions. His preoperative hemoglobin and hematocrit were 15.0 and 42.6 g/dL, respectively, and his electrolytes were normal. His physical examination was otherwise normal. At home the patient took metoprolol 100 mg by mouth once a day. The patient reported that the AICD had discharged twice in the past year during periods of increased physical activity. He did not have any problems with normal physical activity and denied chest pain or shortness of breath on exertion. He denied additional medical history and had never undergone an anesthetic.

After discussion with the patient and his family, the decision was made to perform a brachial plexus block. The AICD was interrogated by the company representative and found to be working properly. We proceeded by performing a right ultrasound-guided infraclavicular brachial plexus block with 40 mL of ropivacaine 0.5% without the use of a nerve stimulator.

Once in the operating room, adhesive external defibrillating pads were placed and the AICD device was turned off due to the expected use of electrocautery during surgery. The patient underwent successful surgery with the brachial plexus block as the main anesthetic and light sedation. Of note, his electrocardiography (ECG) showed premature ventricular contractions throughout the procedure but his hemodynamics were stable throughout. The AICD device was turned back on after the procedure was finished. He recovered well and was discharged home the next morning.

DISCUSSION

This was a challenging case due to the following factors: management of a patient with hypertrophic cardiomyopathy, management of a patient with an AICD *in situ*, the risks of using of peripheral nerve stimulation for performance of a nerve block in patients with AICD, and potential effects on the cardiovascular system of brachial plexus blockade. Careful consideration of each issue separately was important in avoiding complications in this patient. These issues are addressed separately below.

HCM

HCM is a genetic cardiac disorder that is the most common cause of sudden cardiac death in the young[1]. It is characterized by heterogeneous left ventricular hypertrophy and patients often present with diastolic dysfunction that is reflected by elevated left ventricular end-diastolic pressures in spite of often hyperdynamic ventricular function. Clinical course is determined by the following factors: dynamic obstruction to left ventricular outflow, diastolic dysfunction, impaired coronary vasodilator reserve and myocardial ischemia, and supraventricular and ventricular arrhythmias[2]. Anesthetic goals for these patients are: minimize sympathetic activation, expand intravascular volume in order to avoid hypovolemia, and minimize decreases in left ventricular afterload. Reported adverse events for patients with HCM undergoing noncardiac surgery include: congestive heart failure, hypotension, arrhythmias, and myocardial infarction[3].

Our patient had a history of arrhythmias for which he had the AICD placed previously. His electrocardiogram showed sinus arrhythmia and occasional premature ventricular contractions which were concerning. He did not have any history of chest pain and was able to do normal daily activities and work without limitation. The biggest concern was that both episodes where his AICD had discharged previously took place during periods of increased stress and excitement. We all agreed that avoiding a general anesthetic was the best course of action in this case.

AICD

Patients presenting for noncardiac surgery with AICD *in situ* are becoming more common every day. During surgery, the AICD should be deactivated in order to avoid accidental discharge or damage to the device cause by electrocautery or any device that generates a pulse current, including peripheral nerve stimulators[4]. Other patient factors may affect the function of an AICD. Electrolyte abnormalities may cause the actions of an AICD to fail. In addition, patient positioning, positive pressure ventilation, and shivering may affect the functionality of the AICD.

It is important to place external defibrillating pads on the patient while the device is turned off. In our patient, we first applied the external defibrillating pads and turned on the monitoring function of the external defibrillating device. Then, we turned off the AICD device immediately before surgery. Once surgery was finished, we turned the AICD back on and it was found to be functioning properly.

Peripheral nerve stimulation and AICD

Once the decision was made to perform a brachial plexus block in this patient, we needed to take into consideration the potential effects of a nerve stimulator on the AICD device. Manickam *et al*[5] described a set of recommendations with regards to the use of peripheral nerve stimulation in patients with pacemakers. The same issues apply to AICD. If stimulation cannot be avoided, the ground electrode should be placed as far away as possible from the device and stimulation should be done well away from the device (at least 6 inches). Stimulating pulses should be no more than 0.2 milliseconds in duration and the rate of stimulation should not be faster than 1 Hz[5].

Although the surgery and nerve block were to be performed on the right side, away from the AICD, it was decided that it would be best to avoid the use of peripheral nerve stimulation if possible. With the assistance of ultrasound, we were able to visualize the structures and place the local anesthetic around the nerves to provide a surgical block while avoiding the use of nerve stimulation.

Stellate ganglion block after brachial plexus block

Stellate ganglion block is a technique used to diagnose and treat complex regional pain syndrome of the upper extremity. It is performed by local anesthetic injection around the sympathetic chain at the C6 level. Inadvertent blockade of the stellate ganglion may occur during blockade of the brachial plexus and the most common clinical presentation is Horner's syndrome. Horner's syndrome presents as ptosis, miosis and anhidrosis of the ipsilateral face. This commonly resolves within a couple of hours without clinical significance. Reassurance of the patients is all that is needed. A recent study by Tran *et al*[6] found the incidence of Horner's syndrome in ultrasound-guided supraclavicular blocks to be 37%, compared to 5% for infraclavicular and 0% for axillary blocks. However, a report on 510 consecutive ultrasound-guided supraclavicular blocks showed an incidence of Horner's of only 1%[7]. All in all, the more distal blocks have less incidence of this side effect.

Fujiki *et al*[8] studied hemodynamic effects of stellate ganglion block on healthy volunteers. They found that: (1) autonomic innervation of the sinus node is mainly through the right-sided stellate ganglion; (2) pharmacologic right-sided stellate ganglion block may attenuate not only sympathetic but also parasympathetic activity; and (3) following right stellate ganglion block the decrease in both the sympathetic and parasympathetic influence on the sinus node may inconsistently counterbalance and change the RR interval. Left-sided stellate ganglion block changed none of the heart rate variability indices studied.

Although the effects of stellate ganglion blockade on heart rate and electrical conduction may be clinically insignificant in healthy patients, these effects could potentially be detrimental in patients with cardiac disease, especially with history of arrhythmias. Therefore, it is probably best to avoid this side effect in patients with cardiac disease.

We chose an ultrasound-guided infraclavicular block due to our familiarity and success with the technique. Both a supraclavicular and an axillary block would also have been adequate for this surgical procedure. Since the surgery was on the right arm, opposite the AICD device, we were not as concerned with the needle insertion site. If the patient had needed surgery on his left arm, an ultrasound-guided axillary block would have been our choice, as we would want to avoid nerve stimulation and needle placement anywhere near the chest.

In conclusion, a patient with HCM and AICD who required an anesthetic for repair of this hand was successfully managed by placement of an ultrasound-guided brachial plexus nerve block. Consideration of the multiple issues which may arise is important in the management of these patients. Patients presenting for surgery with these medical problems are becoming more and more common. Special consideration should be taken regarding the method of nerve block placement in patient with an AICD in place. Potential hemodynamic effects of anesthetic techniques in patients with HCM and AICD should be considered at all times. Future studies should look at which anesthetic techniques best maintain hemodynamics in patients with HCM and AICD undergoing a variety of surgical procedures.

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CASE REPORT

Management of a patient with perioperative saddle embolus

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Abstract

Pulmonary embolism is a major cause of morbidity and mortality. Risk factors include venous stasis, endothelial injury, and hypercoagulability. Prevention centers on the use of sequential compression devices and anticoagulation in the hospital patient. This is the case of a 45-year-old male who presented for open reduction and internal fixation of tibia plateau fracture. He developed a saddle embolus during the perioperative period which was diagnosed in the recovery room after workup for the cause of his poor oxygenation. A chest computed tomographic scan showed an extensive saddle embolus with partial occlusion of the bilateral main pulmonary arteries and all segmental pulmonary artery branches. This case report discusses his diagnosis, management and clinical course. In addition, risk factors, treatment and prevention for pulmonary embolus and described.

Key words: Venous thromboembolism; Pulmonary embolus; Saddle embolus; Tibia fracture; Anesthesia

Core tip: The case report describes the diagnosis, management and treatment of a 45-year-old male who developed a saddle pulmonary embolus during open reduction and internal fixation of tibia plateau fracture. The incidence of pulmonary embolism, risk factors, and treatment and prevention choices are discussed.

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INTRODUCTION

Venous thromboembolism clinically manifested as deep vein thrombosis and pulmonary embolism, is a common cause of increased morbidity and mortality. Pulmonary embolism (PE) can manifest in a variety of clinical settings ranging from acute shortness of breath in the emergency department to intraoperative cardiovascular collapse, hypoxemia in the recovery room, to respiratory distress in the intensive care unit. In the perioperative setting, it is critical for the anesthesiologist to have a high index of suspicion for PE as symptoms and signs are often vague and non-specific. To do so, one must know the medical and surgical risk factors that can increase the probability of PE as well as the prophylactic measures that can be used to diminish the risk. In addition, it is critical to know the management of pulmonary embolism in the perioperative setting.

CASE REPORT

A 45-year-old African American male was admitted to the hospital with a left tibia plateau fracture after a motor vehicle accident. He had no other injuries from the accident and had no previous medical history other than 20 pack-year history of smoking tobacco. The patient was admitted and started on enoxaparin 40 mg subcutaneously once a day for deep venous thrombosis prophylaxis. On hospital day 3 he underwent open reduction and internal fixation of the left tibia plateau fracture. The surgical procedure was uneventful. A laryngeal mask airway was

used initially, but was subsequently switched to an endotracheal tube after difficulty with placement and difficulty maintaining adequate ventilation and oxygen saturation. After placement of the endotracheal tube, ventilation and oxygenation went back to normal and the procedure proceeded as planned.

The patient was subsequently extubated at the end of surgery. Although he was awake and was ventilating well, he continued to have O_2 saturations in the mid 80 to 90 s with 100% non-rebreather mask along with sustained tachycardia in the 110 to 120 s even after adequate pain control. An arterial blood gas was drawn in the post anesthesia care unit and it showed a pH of 7.40, pCO_2 of 41.6 mmHg, pO_2 of 61.0 mmHg, bicarbonate of 25.1 and oxygen saturation of 91%. A chest X-ray was taken showing an interval development of a right upper lobe opacity concerning for pneumonia or aspiration when compared to his admission chest X-ray. A computed tomography scan of the chest was performed and an extensive saddle embolus with partial occlusion of the bilateral main pulmonary arteries and all segmental pulmonary artery branches with significant thrombus burden. In addition, a right upper lobe dense airspace consolidation with peripheral ground glass opacification along the right posterior segmental bronchus and bronchus intermedius which was suspicious of infarction was found. An echocradiogram was then performed showing a severely dilated right atrium and right ventricle. However, he had normal left ventricular function and his ejection fraction was between 55%-60%. Bilateral lower extremity Doppler studies showed occlusive thrombi in the left common femoral and superficial femoral veins.

The patient was started on a heparin infusion and subsequently had an inferior vena cava filter placed. He remained in the intensive care unit for several days until his oxygen demand was reduced from 100% oxygen *via* non-rebreather mask to nasal cannula. He never required intubation to support his oxygenation and ventilation and remained hemodynamically stable throughout his hospital stay. He was transitioned to the regular nursing floor without need for oxygen supplementation and soon discharged on warfarin with follow up at the Pulmonary and Orthopedics clinics. On follow up, he had returned to normal function and recovered from his surgical procedure well.

DISCUSSION

Our patient was able to fully recover from an event that can often be lethal. It is unknown at which point after his tibia fracture the patient developed his blood clot and pulmonary embolism. We were able to begin treatment as soon as the diagnosis was made. It also helped that our patient was healthy and physically fit before this event took place.

The incidence of mortality after pulmonary embolism has been reported to be as high as 300000 per year[1]. This number understates the significant morbidity including chronic pulmonary hypertension, disability, and impaired quality of life that affects survivors. It is estimated that the economic burden of pulmonary embolism is greater than $1.5 billion a year in healthcare costs with estimates stating that each pulmonary embolism results in additional healthcare costs in excess of $30000[1]. The three-month mortality of pulmonary embolism has been stated as high as 15%-18%[1]. While most patients with acute pulmonary embolism survive, possible long term sequelae include chronic thromboembolic pulmonary hypertension and chronic leg pain and swelling.

It is important for all medical personnel to be aware of patients at higher risk for developing venous thromboembolic disease. Risk factors that acutely increase the risk of pulmonary embolism include orthopedic surgeries, especially total hip and knee replacement, surgery for hip fractures, as well as trauma and spinal cord injuries. Acute medical morbidity, especially malignancy is also a major risk factor.

A good approach to understanding all the risk factors that predispose patients to pulmonary embolism is to understand Virchow's triad[2]. Virchow's triad states that venous stasis, endothelial injury, and hypercoagulability will increase the risk of thrombosis[2]. Venous stasis can occur when patients are immobile (*i.e.*, spinal cord injury, trauma, orthopedic fractures) or when there is a problem with the pump (*i.e.*, heart failure). Surgical procedures are a major culprit to endothelial injury, as are invasive catheter-based procedures including angiograms and placement of transvenous pacemakers. Hypercoagulability can be hereditary such as deficiency or mutation of certain factors (prothrombin, protein C, protein S) or from pro-inflammatory states (malignancy, myeloproliferative syndromes, antiphospholipid antibodies, hyperhomocysteinemia, heparin-induced thrombocytopenia, acquired immunodeficiency syndrome (AIDS), burns, lupus, oral contraceptives)[1].

Orthopedic patients have a high risk from development of deep vein thrombosis and pulmonary embolism. A study by Geerts *et al*[3] showed an incidence of deep venous thrombosis (DVT) of 69% in patient with lower extremity fractures. This made our patient with a tibia fracture at high risk for development of DVT. As is customary with most trauma patients at our hospital, he was on enoxaparin for DVT prophylaxis up until the morning of his surgery. However, it did not prevent him from developing a saddle pulmonary embolus.

When acute pulmonary embolism is present, parenteral anticoagulation with either low molecular weight heparin or unfractionated heparin should be administered, unless contraindicated[4,5]. The primary indications for placement of an inferior vena cava filter are contraindications to anticoagulation, risk of major bleeding during anticoagulation, and recurrent embolism while receiving adequate therapy[4]. Filters are also considered in cases of massive pulmonary embolism, with the thought being that additional thrombotic burden may be life threatening. In cases of massive pulmonary embolism with cardiovascular collapse, requiring cardiopulmonary

resuscitation and blood pressure support, mortality is much higher. A retrospective review performed at Texas Heart Institute by Konstantinov *et al*[6] showed that emergency treatment using cardiopulmonary bypass may be beneficial. Rapid recognition and treatment are very important to prevent severe morbidity and mortality after pulmonary embolism.

Current methods used to prevent DVT and PE have significantly reduced the incidence of fatal PE[7]. Treatments that combine mechanical prophylaxis such as, sequential compression devices or inferior vena cava filters, with low molecular weight heparin appear to be most effective[7]. However, even patients on appropriate prophylaxis are still developing DVT and PE. Future research will hopefully help with better prevention and treatment of pulmonary embolism.

In conclusion, we presented the case of a 45-year-old male who developed a saddle pulmonary embolism after tibia fracture during the perioperative period. Prompt diagnosis and treatment prevented morbidity and mortality in this patient.

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Write as mean ± SD or mean ± SE.

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Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

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