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RESEARCH

Intravenous paracetamol — waste not, want not: a retrospective audit on the appropriate use of intravenous paracetamol at Universitas Academic Hospital Complex—Bloemfontein

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Background: Paracetamol can be given both orally and intravenously (IV) with similar clinical efficacy, but the IV formulation is 360 times more expensive. IV paracetamol is therefore only recommended when the oral route is not available. This study investigated whether IV paracetamol was being used appropriately and whether there had been a change in prescribing patterns between 2008 and 2015 after the introduction and update of a prescribing protocol at an academic hospital complex in Bloemfontein, South Africa.
Methods: A retrospective comparative audit of patient files was undertaken. The prescribing and administration habits of IV paracetamol were compared for two consecutive months, seven years apart, including 88 and 83 patients, respectively, who had received IV paracetamol.
Results: IV paracetamol was administered appropriately in 37.5% of patients in 2008 and in 43.4% of patients in 2015 ($p = 0.43$). There was an improvement in the duration that IV paracetamol was prescribed for, which decreased from a median two days in 2008 to one day ($p < 0.01$) in 2015. In total, 55 (32.4%) patients had a concomitant oral and IV paracetamol prescription, of which 37 (21.6%) patients also received concomitant paracetamol administration. Twenty patients exceeded the 24-hour maximum dose. Seventeen patients weighed less than 40 kg; six of these patients (three paediatric and three adult) did not receive the correct weight adjusted dose of paracetamol, 15 mg/kg, resulting in excessive doses of paracetamol being administered (21–32.3 mg/kg).
Conclusions: Patients are receiving IV paracetamol when the oral route is available; this is an unnecessary waste of money. Excessive doses of paracetamol were administered due to concomitant oral and IV paracetamol prescription and administration, and a failure to calculate dose of paracetamol according to body weight in low body weight patients. Further remedial interventions are therefore required.

Keywords: acetaminophen, analgesia, appropriate, audit, intravenous, pain, paracetamol, pyrexia

Introduction

Paracetamol is the most frequently used analgesic and antipyretic worldwide.[1] It has been used widely for over 100 years and has a good safety record, with most problems occurring only if excessive doses are used.[2,3] Paracetamol is a synthetic non-opioid drug acting on both peripheral and central pain pathways, with minimal anti-inflammatory properties.[4–6]

Various preparations of paracetamol exist which can be administered via several different routes—oral, rectal and intravenous (IV).[7] The most commonly used route for administration is the oral route. Paracetamol administered via the oral route has a slower onset of analgesia (approximately 45 minutes) when compared with the IV route (20 minutes), but thereafter the clinical effect is similar. The bioavailability of paracetamol when administered via the rectal route is approximately 60% and is the lowest among the several administration routes.[8,9] Surgical patients expect effective and fast-acting pain relief. When the oral route of administration is not possible or rapid analgesia is needed, IV administration is the route of choice.[10]

Concerns have been raised that IV paracetamol is not always appropriately prescribed, as its use is associated with the following problems:[11–14]

- increased relative costs (R0.10 per 1 gram (g) oral paracetamol versus R36.48 per 1 g IV paracetamol) and nursing time;
- potential for overdose with concomitant oral drugs containing paracetamol;
- failure to adjust the dose according to body weight or other patient factors;
- increased risk of infection with repetitive prolonged administration due to the IV cannula remaining in situ.

Acute pain management guidelines published in the United States and in the South African Society of Anaesthesiologists' (SASA) *South Africa Acute Pain Guidelines* recommend the oral administration of drugs as soon as the patient is able to tolerate them.[15,16] Obtaining an early switch from the IV to the oral route of administration of paracetamol in the management of pain therefore seems a reasonable step as both have been shown to be effective and safe, thus reducing the number of paracetamol injections per patient.

Universitas Academic Hospital Complex (UAHC) is a tertiary hospital, located within central South Africa, Free State, Bloemfontein. IV paracetamol was first introduced to the hospital on 21 April 2008, with a paediatric dose only becoming available on 30 March 2011. A protocol for using IV paracetamol was first disseminated in 2008 in UAHC. A revision of the policy was made in 2014 and two addendums regarding important safety information were added in 2015.[17] Within the various state hospitals in Bloemfontein, Pelonomi Hospital, which is also a tertiary hospital, has limited the use of IV paracetamol in that it may be prescribed only by an anaesthesiologist. UAHC has a protocol limiting the duration of IV paracetamol use to a 24-hour period or four doses. It may also only be prescribed by a specialist in the intensive care unit (ICU), anaesthesiology or theatre.

The primary objective of this study was to investigate whether IV paracetamol was being used appropriately at UAHC after the introduction of an IV paracetamol protocol in 2008, which was revised in 2015. Appropriate IV paracetamol use was defined as IV paracetamol prescribed to patients not able to receive or tolerate oral paracetamol, for the correct indication, at the correct dose, and for the correct duration. Secondary objectives included a review of the characteristics of the IV paracetamol prescriptions and a review of patients whose prescriptions exceeded the daily maximum dose of 4 grams.

Method

This study was a retrospective comparative audit. Two consecutive months were selected in two different years using a random number chart in order to be compared (June to July 2008 and July to August 2015). The pharmacy was able to provide a list of patients who received IV paracetamol during these two-month periods using the Meditech software system (https://ehr.meditech.com/international/meditech-south-africa). Data were collected from patient records within the hospital archive. All patients who received a dose of IV paracetamol during the study period were included in the study. Patients excluded from the study were patients with incomplete or illegible medical records and patients not yet discharged from the hospital.

Data collected consisted of four components:

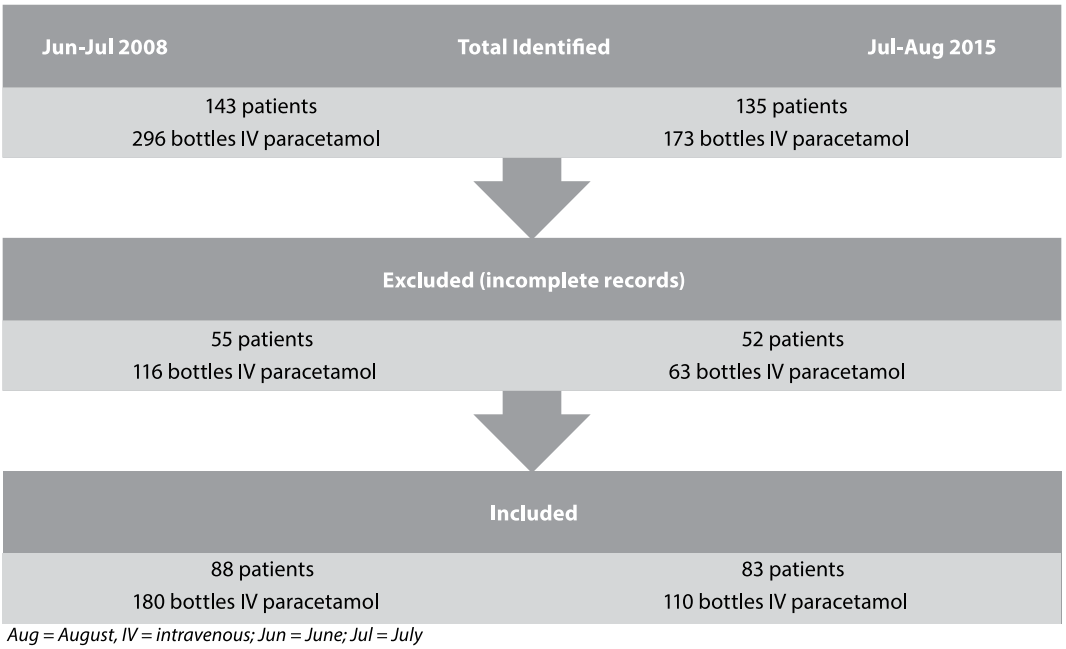
(1) demographics: age, weight, gender, admission and discharge date, admission diagnosis, ward and surgery type;
(2) prescribing information: indication, dose, duration, administration and concomitant paracetamol prescription;
(3) IV administration information: dose and duration of administration;
(4) clinical information: NPO/fasted, postoperative time to swallow, nasogastric tube in situ, and whether antiemetic medications were prescribed and administered.

Analysis was performed by the Department of Biostatistics, Faculty of Health Sciences, University of the Free State (UFS). Categorical variables were summarised as frequencies and percentages. Numerical variables were summarised as means and standard deviations or medians with interquartile ranges (IQR). The two time-periods were compared statistically using Mann–Whitney tests for numerical variables and chi-square or Fisher's exact test for categorical variables. *P*-values ≤ 0.05 were considered statistically significant. A 95% confidence interval (CI) was calculated for the main outcome.

Results

During the combined four-month study period, a total of 469 1 g IV paracetamol bottles were issued to 278 patients. Incomplete records were found for 107 patients. A total of 171 patients, who received 290 bottles of IV paracetamol, were included in the study (Figure 1).

Patient characteristics are given in Table 1. The median patient age was 48.5 years in 2008 and 39 years in 2015. Paediatric vials of IV paracetamol were not available in 2008, but were available in 2015. In all, 18 paediatric patients received IV paracetamol, 11 in 2008 (from adult vials) and seven in 2015. The patient weight and gender were similar between the two groups.



Aug = August, IV = intravenous; Jun = June; Jul = July

Figure 1: Flow diagram of identified, excluded and included records.

The duration of hospital stay was similar between the two groups: a median of 10 days in 2008 and 8 days in 2015 ($p = 0.29$). The number of patients who underwent surgery was also similar between the two groups: 78 (88.6%) patients in 2008 and 77 (92.8%) patients in 2015 ($p = 0.08$).

There was no significant difference in the IV paracetamol dose prescribed in mg/kg between the two groups (Table 2). In 2008, IV paracetamol was prescribed for a median of two days, which decreased to a median of one day in 2015 ($p < 0.01$). The duration of all IV analgesics prescribed also showed a decrease, from a median of three days to two days ($p = 0.02$).

There were 11 patients in 2008 and six patients in 2015 who had a weight of < 40 kg. Five of these patients in 2008, of whom three were paediatric patients, did not have the correct weight-adjusted dose. In 2015, only one patient did not have the correct weight-adjusted dose. This resulted in doses of 21–32.3 mg/kg being administered to these patients.

As shown in Table 3, IV paracetamol was administered appropriately in only 33 (37.5%) patients in 2008 and 36 (43.4%) patients in 2015 with no significant difference between the year groups (95% CI –8.8%; 20.6%).

The six-hourly dosing frequency of IV paracetamol changed significantly between 2008 ($n = 79$, 89.7%) patients and 2015 ($n = 60$, 72.3%) patients ($p < 0.01$). An increase in the eight-hourly prescriptions was also observed from five (5.6%) patients in 2008 to 21 (25.3%) patients in 2015.

There were 69 (78.4%) patients in 2008 and 72 (86.8%) in 2015 who were able to swallow within 24 hours post-surgery ($p = 0.03$). Of the patients who could swallow within 24 hours, 48 (54.5%) patients in 2008 and 47 (56.6%) patients in 2015 received IV paracetamol.

Antiemetic medication was prescribed in 29 (33.0%) patients in 2008 and 42 (50.6%) patients in 2015 ($p = 0.02$). Forty (23.0%) patients had a nasogastric tube in situ and were receiving nasogastric fluids/feeds when they received a dose of IV paracetamol. Patients who had a nasogastric tube in situ while receiving IV paracetamol were located in the various ICUs (multidisciplinary, neurosurgical, surgical, paediatric and cardiothoracic) and the high care units—maternity high care and general high care.

Overall, 55 (32.2%) patients had two separate paracetamol prescriptions, 28 (31.9%) in 2008 and 27 (32.5%) in 2015. Of these separate paracetamol prescriptions, 37 (21.6%) patients also received a concomitant paracetamol administration on the same day—21 (23.8%) in 2008 and 16 (19.3%) in 2015. Twenty (11.7%) patients, nine (10.2%) in 2008 and 11 (13.3%) in 2015, exceeded the 24-hour maximum dose of 4 grams or 60 mg/kg/24 hours. Examples of patients who received a dose of paracetamol exceeding the maximum daily limit are given in Table 4.

Table 1: Characteristics of patients receiving intravenous (IV) paracetamol during 2008 and 2015

Demographic characteristics	2008 (*N* = 88)	2015 (*N* = 83)	*p*-value
Median age in years (IQR)	48.5 (25–65)	39 (26–55)	0.16
Median weight in kg (IQR)	68 (46–83)	65 (55–82)	0.57
Gender:			0.57
Male *n* (%)	42 (47.7)	36 (43.4)	-
Female *n* (%)	46 (52.3)	47 (56.6)	-

Note: IQR = interquartile range.

A total of 95 (55.6%) patients received IV paracetamol for longer than 24 hours, 55 (62.5%) in 2008 and 40 (48.2%) in 2015. In 2008, all the wards had one or more prescriptions for IV paracetamol administered for a duration of greater than 24 hours. Wards with a prescription for a duration of greater than 24 hours in 2015 were cardiothoracic, ICU (paediatric, multidisciplinary and neurosurgical), maternity high care, maternity, vascular, hepatobiliary, gastroenterology, ear, nose and throat, and plastic surgery.

In both year groups, the prescribing physician was mostly a registrar: 144 patients (84.2%) (Table 5).

Discussion

This audit has shown that IV paracetamol has been inappropriately prescribed and administered. The hospital complex has a protocol regarding the use of IV paracetamol and this study has demonstrated poor compliance with the appropriate use of IV paracetamol.

Reasons for the non-compliance of the IV paracetamol policy may be the following:

- IV paracetamol is not being prescribed by specialists but by junior doctors:

The pharmacy does not have the resources to monitor all IV paracetamol prescriptions. Clarity regarding a 'specialist in theatre' as indicated in the protocol also remains uncertain.

- Poor prescribing habits:

Doctors may not be aware of the IV paracetamol protocol and are non-compliant.

IV paracetamol scripts were written in such a manner that a patient could receive 3–4 doses for a 24-hour period, with no emphasis on the patient's ability to tolerate oral liquids/food. This included the scripts for the perioperative period, protocols displayed for epidurals and patient-controlled analgesia pumps. This practice should be changed, emphasising that as soon as the patient can tolerate oral liquids/feeds that the administration of IV paracetamol be changed to oral paracetamol. (Most patients who were fasted perioperatively were able to tolerate oral liquids/feeds within 24 hours).

IV paracetamol is prescribed for a duration of greater than 24 hours.

- Convenience of using IV paracetamol:

Patients may be more satisfied after receiving IV paracetamol drug compared with an oral drug and placebo.[18]

- The rectal route of administration is no longer used at UAHC when the oral route of administration is unavailable.
- Increased doctor awareness of the availability of IV paracetamol.

A similar audit by Palmer *et al.*[12] at a tertiary paediatric hospital in Australia was performed when IV paracetamol was introduced to the hospital. IV paracetamol was placed conditionally on the hospital formulary with prescribing rights limited to two senior clinicians and for restricted indications Despite the limited prescriber rights there were still deviations from the guidelines, which were not associated with adverse events. The strict compliance during the introductory period allowed the Drug

Table 2: Intravenous (IV) paracetamol dose and duration of prescriptions and duration of all IV analgesics

	2008 (*N* = 88)		2015 (*N* = 83)		*p*-value
Prescription characteristic	**Median**	**Range**	**Median**	**Range**	
IV paracetamol dose prescribed (mg/kg)	17.5	1–31	17.5	2–27.5	0.47
IV paracetamol duration prescribed (days)	2	1–23	1	1–10	< 0.01
Duration of all IV analgesics prescribed (days)	3	1–23	2	0–10	0.02

Table 3: Intravenous (IV) paracetamol prescription characteristics

Characteristic	**2008 (*N* = 88)**	**2015 (*N* = 83)**	***p*-value**
	***n* (%)**	***n* (%)**	
Indication for paracetamol:			0.14
Analgesia	73 (82.9)	78 (94.0)	
Pyrexia	8 (9.1)	2 (2.4)	
Analgesia and pyrexia	5 (5.7)	2 (2.4)	
Not documented	2 (2.3)	1 (1.2)	
Indication for IV administration:			0.58
NPO (peri-operative)	73 (83.0)	73 (88.0)	
Emesis	3 (3.4)	4 (4.8)	
Unconscious (low GCS)	5 (5.7)	3 (3.6)	
Not documented	7 (7.9)	3 (3.6)	
IV frequency of administration:			< 0.01
Stat (immediately)	3 (3.3)	2 (2.4)	
q4 h (4-hourly)	1 (1.4)	0 (0)	
q6 h (6-hourly)	79 (89.7)	60 (72.3)	
q8 h (8-hourly)	5 (5.6)	21 (25.3)	
Post-surgical time to swallow (hours):			0.03
≤ 6	32 (36.4)	36 (43.4)	
> 6 ≤ 12	9 (10.2)	17 (20.5)	
> 12 ≤ 24	28 (31.8)	19 (22.9)	
> 24 ≤ 48	9 (10.2)	10 (12.1)	
> 48 ≤ 72	6 (6.8)	0 (0)	
> 72	4 (4.6)	1 (1.2)	
IV was followed by oral paracetamol	74 (84.1)	75 (90.4)	0.22
Concomitant paracetamol prescription	28 (31.8)	27 (32.5)	0.92
Concomitant paracetamol administration	21 (23.9)	16 (19.3)	0.47
Daily max exceeded (4 g/24 hours)	9 (10.2)	11 (13.2)	0.54
Antiemetic prescribed	29 (33.0)	42 (50.6)	0.02
Antiemetic administered	25 (28.4)	29 (34.9)	0.36
NG in situ	22 (25.0)	18 (21.7)	0.61
Appropriate IV paracetamol administration	33 (37.5)	36 (43.4)	0.43

Notes: IV = intravenous; GCS = Glasgow Coma Scale; NG = nasogastric; NPO = nil per os.

Use Council to extend prescribing rights to consultants and trainee anaesthetists with limited indications within the institution.

IV paracetamol is indicated as an antipyretic and analgesic for symptomatic relief of mild to moderate pain and is used on all levels of the World Health Organisation analgesic ladder.[19,20] In a recent literature review of randomised clinical trials for acute postoperative pain, the data indicated that IV paracetamol is an effective analgesic across a variety of surgical procedures.[21–26] The absorption of orally administered paracetamol may be unreliable perioperatively, up to 72 hours postoperatively. This may be due to delayed gastric emptying from the patient being stressed, preoperative fasting, concomitant opioid administration, the long-lasting effects of anaesthesia and the surgery itself.[27,28]

All drugs that can be administered via the oral route, except those in a slow-release formulation, may be administered via a feeding tube.[29–31] Emphasis should be made regarding administering oral paracetamol via the nasogastric tubes in the various ICUs. If a patient is able to absorb the nasogastric fluids/feeds, they should tolerate nasogastric paracetamol. Some patients with poor absorption from the gastrointestinal tract may require prolonged use of IV paracetamol. Dedicated syringes should be used for nasogastric tubes that are labelled and cannot be used with the IV system.

In adults, paracetamol has a ceiling effect at a dose of 1 000 mg, so a further increase in the dose will not result in a further increase in analgesia, but will increase the side effects and potential for toxicity.[32,33] Paracetamol has intermediate lipid solubility, therefore an increase in the patient's body-fat proportion alters the distribution slightly. At present, there is no evidence that this alteration is significant or affects the analgesic and antipyretic efficacy. There is thus no rationale for more than 1 g or two preparations (oral and IV) being prescribed concurrently.[34]

The Food and Drug Authority (FDA) issued a notice in 2014 stating that all prescription drug products with more than 325 mg of acetaminophen be discontinued in order to protect consumers from liver damage.[35] Patients who had concomitant paracetamol prescription and administration had paracetamol prescribed under the various trade names (Perfalgan®, Panado® and Dolorol Forte®). Despite the prescribing doctor being familiar with the generic and trade names, the staff in the wards who administer the paracetamol may not be familiar with the various names. It should be emphasised that generic names and not trade names are used when prescribing any drugs, including IV paracetamol, in order to avoid concomitant administration. Prescriptions should also include the maximum daily dose and be for a limited duration.

Paracetamol is known to have a narrow therapeutic index. The objective of this study was not to assess the toxicity from paracetamol but to audit how IV paracetamol is prescribed and administered. Liver function was not assessed so the clinical impact of the higher than recommended doses prescribed is not known.

From this study, there is clearly confusion among prescribing doctors regarding the various appropriate dose-per-weight and dose-per-age schedules. The British National Formulary and

Table 4: Examples of patients who received a dose of paracetamol exceeding the daily maximum limit

Two separate paracetamol prescriptions	Age (years)	Patient weight (kg)	Dose (grams received /24 hours)	Dose (mg/kg received /24 hours)	Duration received (days)	Prescribed names of the combination of drugs
Yes	3	19	1.3	68.4	1	Perfalgan® & Dolorol Forte®
Yes	12	35	4	114.2	1	Perfalgan & Dolorol Forte®
Yes	12	77	6	78	1	Perfalgan® & Dolorol Forte®
Yes	12	55	5.1	93	1	Perfalgan® & Panado®
Yes	22	40	5	125	2	Perfalgan® & Panado®
Yes	26	100	7	70	1	Perfalgan® & Panado®
Yes	27	52	4.5	86.5	3	Perfalgan® & Dolorol Forte®
Yes	38	92	5	54.3	1	Perfalgan® & Panado® syrup
Yes	38	88	5	56	1	Perfalgan® & Panado®
Yes	38	88	6	68	2	Perfalgan® & Panado®
Yes	54	58	5	86	1	Perfalgan® & Dolorol Forte®
Yes	40	58	5	86.2	1	Perfalgan® & Panado®
Yes	44	66	5	76	1	Perfalgan® & Panado®
Yes	51	99	5	50	1	Perfalgan® & Dolorol Forte®
Yes	53	60	8	133.3	2	Perfalgan® & Dolorol Forte®
Yes	54	43	5	116.2	5	Perfalgan® & Dolorol Forte®
Yes	58	120	6	50	2	Perfalgan® & Perfalgan®
No	64	60	7	117	1	Perfalgan® & Dolorol Forte®

Table 5: Rank of the doctor prescribing intravenous (IV) paracetamol and rank of doctors who prescribed IV paracetamol for a duration of > 24 hours

Factor	2008	2015	*p*-value
Rank of doctor	*n* (%)	*n* (%)	
Prescribed IV paracetamol:	(*n* = 88)	(*n* = 83)	< 0.01
Intern	4 (4.5)	8 (9.6)	
Medical Officer	13 (14.8)	1 (1.2)	
Registrar	71 (80.7)	73 (88.0)	
Consultant	0	1 (1.2)	
Prescribed IV paracetamol for a duration of > 24 hours:	(*n* = 55)	(*n* = 40)	0.02
Intern	1 (1.8)	3 (7.5)	
Medical Officer	10 (18.2)	1 (2.5)	
Registrar	43 (78.2)	36 (90.0)	
Consultant	1 (1.8)	0 (0)	

SASA Acute Pain Guidelines recommend the maximum daily infusion doses listed in Table 6.[5,36]

It is recommended that the dose be decreased to 15 mg/kg in adults weighing less than 50 kg. Due to the potential for toxicity with using the 1 g in 100 ml vial of IV paracetamol, the United Kingdom Medicines and Healthcare Products Regulatory Agency (MHRA) has indicated that only 50 ml with 500 mg vials is to be used in patients weighing less than 33 kg.[37,38]

An audit on the use of IV paracetamol in infants under one year of age in the United Kingdom and Ireland demonstrated that paracetamol dosing is frequently above the licensed dose and is outside the licenced age range, but is in keeping with pharmacokinetic studies.[39]

During the total audit period, at least 102 patients were administered 174 bottles of IV paracetamol inappropriately. This amounts to a cost of R6 333.60 (R36.48/1 g), with the equivalent cost of oral paracetamol being R17.40 (R0.10/1 g). Additional to the extra cost of the ampoules of the IV paracetamol is the cost of maintaining the IV cannula, nursing staff and monitoring the infusion.

Limitations

This study was a retrospective audit, relying on patient records. Many patients were excluded due to the poor quality of patient records (38% of the IV bottles issued from the pharmacy had inadequate records for inclusion in the study).

Only prescribing and administration information was audited, not the actual clinical impact of patients at risk for potential overdose. Despite the introduction and dissemination within the

Table 6: Intravenous (IV) paracetamol dosing guidelines[5,36]

	Dose of IV paracetamol (per infusion administration)	Interval between each administration	Maximum daily infusion dose
Preterm neonates > 32 weeks' postmenstrual age (controversial)	7.5 mg/kg	8 hours	25 mg/kg
Term, newborn, infants, toddlers and children weighing < 10 kg	7.5 mg/kg	4–6 hours	30 mg/kg
Children weighing 10–33 kg	15 mg/kg	4–6 hours	60 mg/kg
Children, adolescents and adults weighing 33–50 kg	15 mg/kg	4–6 hours	60 mg/kg
Adolescents and adults weighing > 50 kg	1 g	4–6 hours	Must not exceed 4 g

hospital regarding the IV paracetamol prescribing protocol, no training was initiated regarding these updates.

Patients' records for the dosing administration intervals were not monitored, i.e. whether a paracetamol dose was administered within four hours of the previous paracetamol dose. Only the 24-hour total dose of paracetamol was monitored. IV paracetamol that was administered intraoperatively was also not monitored or compared with when the next dose of paracetamol was received in the ward.

Conclusion

IV paracetamol is not being used appropriately, as the guidelines regarding its use are not being adhered to. The implications of inappropriate IV paracetamol use can be divided into the following categories:

- potential for patient overdose (concomitant administration);
- economic implications to the hospital.

Additional training regarding the appropriate use of IV paracetamol should be given to the relevant prescribing staff. Protocols with the various dosing schedules according to age and weight should be visually displayed in common prescribing areas. In order to avoid concomitant paracetamol administration, prescriptions for paracetamol and all drugs should be done using the generic name and not the trade name. This will avoid confusing ward staff who administer paracetamol with all the various trade names. Prescriptions should include the daily maximum dose of paracetamol and emphasise the need to stop the IV route of administration as soon as the patient can tolerate oral liquids/feeds. Standard anaesthetic practice should entail documenting on the ward prescription when a dose of IV paracetamol was administered intraoperatively and when the next dose can be administered in the ward.

Authors' contributions – N.J.P. was the main researcher, completing the project for his MMed (Anaesthesiology) degree. He developed the protocol, did the data collection for this study and wrote up the research. G.L. provided supervision and guidance. G.J. assisted with the protocol development, data analysis, interpretation and write-up.

Ethics approval – This study was approved by the Ethics Committee of the Faculty of Health Sciences of UFS (ECUFS 143/2015). Permission was also obtained from the Free State Department of Health Research Council (FS 2015RP59 690).

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