REVIEW ARTICLE

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Paracetamol: a review with specific focus on the haemodynamic effects of intravenous administration

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ABSTRACT

Paracetamol is one of the most commonly used drugs worldwide with non-prescription sales exceeding 25 thousand million doses per year in the United States of America. The haemodynamic effects of the intravenous paracetamol formulations are largely understudied. There is an emerging body of evidence suggesting that intravenous paracetamol may cause iatrogenic hypotension. Little is known as to the mechanisms of this phenomenon or if intravenous paracetamol indeed does cause hypotension. As paracetamol has negligible solubility in aqueous solutions, many of the commercially available intravenous formulations contain mannitol (up to 3.91 g/100 mL paracetamol) as a stabilising ingredient. It is unknown if mannitol is a contributing factor in the observed hypotension. In this review, we outline the development of paracetamol's current intravenous formulations, describe the composition of these formulations, and overview the literature pertaining to the proposed phenomenon of paracetamol-induced altered hypotension. Understanding the pharmacokinetic and pharmacodymanic properties of intravenous paracetamol may have important clinical implications for vulnerable patients in subgroups where haemodynamic stability is at risk such as those undergoing elective and emergency surgery.

Keywords: *Intravenous, paracetamol, acetaminophen, haemodynamic, blood pressure.*

INTRODUCTION

Paracetamol (also known as Acetaminophen) is an antipyretic, non-opioid analgesic, and non-steroidal anti-inflammatory drug (NSAID), and is one of the most commonly used medications worldwide. Paracetamol was first used clinically in 1893, then avoided for more than 60 years due concerns about paracetamol induced methaemoglobinaemia (1). Subsequently, three separate research groups disproved the toxicity theory (2-4) and paracetamol was released in the United States in 1950 as an oral formulation. It is now used ubiquitously in both prescription and over-the-counter formulations with over 200 million prescriptions annually in the USA, and non-prescription sales exceeding 25 thousand million doses per year, making it the most commonly dispensed pharmaceutical in America (5).

Despite its popularity, the exact mechanism of action of paracetamol is still a matter of debate. Several theories have been proposed, the most consistent being that it acts in a similar fashion to NSAIDs by the inhibition of the cyclo-oxygenase pathways. However, paracetamol lacks both

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the peripheral anti-inflammatory and antiplatelet response seen with NSAIDs (6). More recently, it has been suggested that paracetamol may also be linked with both direct and indirect stimulation of the cannabinoid, nitric oxide synthase, and serotonergic pathways. The overall consensus is that paracetamol has a central site of action with little if any peripheral effect. It is likely that paracetamol has a multifactorial mechanism of action, which may include the activation of different pain pathways hence the difficulty in elucidating its precise mechanism of action. Nevertheless, at the recommended doses, paracetamol possess effective antipyretic and analgesic effects with limited adverse events. For these reasons, it is considered safe for public use. Intravenous (IV) paracetamol was first introduced in the hospital setting in 1985 (7) and indicated when enteral administration is not possible (8). Therefore, the majority of patients receiving IV paracetamol are critically ill and surgical patients. Whilst recent studies suggest an increase in the use of IV paracetamol, there is a paucity of prospective controlled studies demonstrating its efficacy and safety in surgical and critically ill patients (9). This highlights a reliance on paracetamol's existing safety profile, which is largely based on its oral formulations. It is therefore imperative to identify any differences between the formulations as well as unknown side effects that are unique to IV paracetamol. Recently, in the context of critical illness, emerging clinical data has suggested that IV paracetamol may cause hypotension (8, 10-16). This may have important clinical implications for patients who receive IV paracetamol especially critically ill patients, or those undergoing elective and emergency surgery, cohorts where adequate maintenance of haemodynamics reduces the risk of morbidity (17). In this review we outline the development of paracetamol's current IV formulations, with a specific focus on the proposed phenomenon of paracetamol-induced altered haemodynamics. Understanding the pharmacokinetic and pharmacodymanic properties of IV paracetamol may have important clinical implications for vulnerable patients in subgroups where haemodynamic stability is at risk such as those undergoing elective and emergency surgery.

METHODS

Information pertaining to the IV formulations of paracetamol was identified by conducting a thorough literature search of Pubmed, Medline (via Ovid), and Embase (via Ovid), pharmacology textbooks and online sources. Only articles in the English language and human studies were considered. Date restrictions were not applied to the Pubmed and Medline searches. The last search update was in January 2015. The search terms used in the electronic databases are summarized in *Table 1*. Specifically

Table 1 - *Electronic search strategy. Tabular representation of the search strategy combining one term from each column.*

Mode of administration	Drug name	Drug effect
IV	Paracetamol	Haemodynamic
Intravenous	Acetaminophen	Hemodynamic
Parenteral	Panadol	Blood pressure
	Tylenol	Adverse event
	Perfalgan	Adverse effect
	Ofirmev	Side effect

clinical information relevant to the phenomenon of paracetamol-induced altered haemodynamics was included. Screening of titles and abstracts against the inclusion criteria resulted in 81 references retrieved for full-text analysis. Thereafter reference lists were examined resulting in the further inclusion of references from online sources and pharmacology textbooks. A total of 50 articles were included in this review.

The intravenous formulations

The pharmacological importance of paracetamol has been established by the vast number of non-prescription and prescription formulations available. Whilst the oral route of paracetamol administration is common in the hospital setting, its clinical application is limited to subgroups such as critically ill, heavily sedated, anaesthetised or postoperative patients. The rectal route may be used in this setting, however rectal suppositories have an unpredictable bioavailability of 24-98 %, similar to that of the oral formulation bioavailability of 63-89 % (18). Secondly, the placement of the rectal suppository has been implicated as a mechanism for its variable absorption and metabolism due to the different drainage pathways of the rectum (19). Drugs placed in the distal portion of the rectum drain into the general circulation, while drugs are subjected to the hepatic first-pass effect if placed in the proximal rectum. Inconsistencies in the placement and clinical efficacy of paracetamol suppositories have prompted the American Academy of Paediatrics to advocate the use of other methods of administration (20). Importantly, accurate dosing adjustments in the event of early expulsion of the suppository are complicated by the potential for uneven distribution of the active drug throughout the suppository and its availability only in fixed doses. Finally, rectal administration can be considered unpleasant, inconvenient and intrusive. As a result of these limitations, a major advancement in the clinical use of paracetamol has been the introduction of the IV formulations, all of which have a bioavailability of 100 %.

IV Propacetamol

In its raw form, paracetamol has negligible solubility in water and, in aqueous mediums; it is highly sensitive to oxygen and light. As a result, the first formulation of IV paracetamol contained the active ingredient propacetamol hydrochloride. Intravenous propacetamol was produced by Bristol-Myers Squibb, France, in 1985 under the trade name Pro-dafalgan. Propacetamol is rapidly hydrolysed in a 1:1 ratio to produce paracetamol and N,N-diethylglycine by non-specific plasma esterases. Every 2 g of propacetamol yields a total of 1g paracetamol. Pro-dafalgan vials consist of a white, odourless crystalline propacetamol powder that requires reconstitution in a solvent such as glucose, water or sodium citrate. In solution, propacetamol is unstable and requires immediate infusion after reconstitution to avoid degradation. It was found to be an efficacious antipyretic and analgesic, able to produce a faster response compared to oral and rectal formulations (21). However, in the 1990s, several reports of contact dermatitis, due to the skin-sensitizing effects of the phenyl ester N,N-diethylglycine, and complaints of pain on infusion, prompted reconsideration of Pro-dafalgan (22). Its use has since been discontinued in medical practice.

Intravenous paracetamol

In 2002, the first true form of IV paracetamol was introduced by Bristol-Myers Squibb under the trade name Perfalgan. It is a ready-to-use injectable that requires no reconstitution and lacks the undesirable effects of the previous formulation. In order to create a reliable formulation

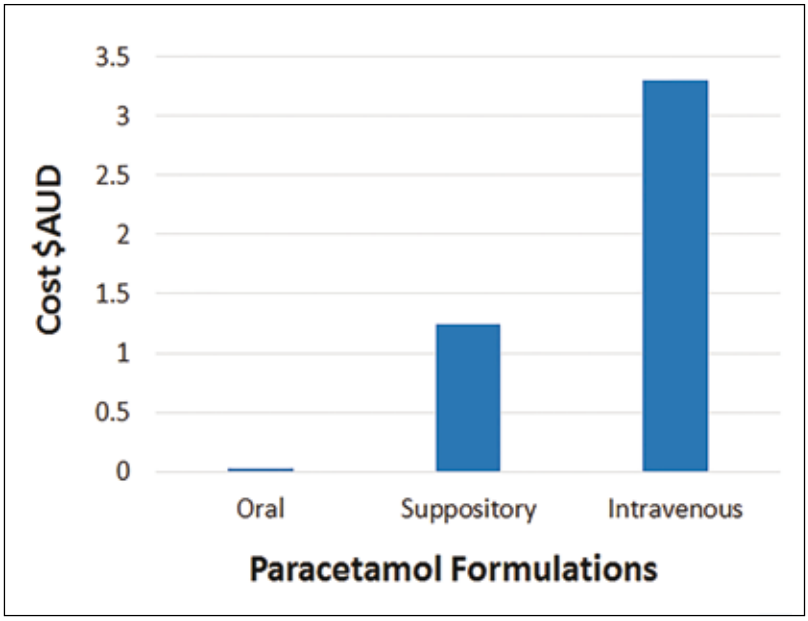

Figure 1 - *The cost difference between the 1000 mg paracetamol formulations.*

of IV paracetamol, the issue of stability present in the propacetamol formulation needed to be addressed. During degradation, paracetamol is converted to 4-aminophenol, which is rapidly converted to the hepatotoxic substance N-acetyl-p-benzoquinoneimine (NAPQI). Paracetamol must be synthesized within an optimum pH range of 5-6 to avoid a hydrolysis reaction and thus conversion to 4-aminophenol. Secondly, chemical oxidation reactions must be avoided. This is managed by bubbling nitrogen into the IV formulations to reduce the amount of oxygen present and by the strict adoption of hermetically sealed oxygen-impermeable glass vials filled with a ready-to-use formulation that does not require reconstitution from an external ampoule. A bioequivalence study performed by Flouvat et al. found a linear pharmacokinetic relationship between 1g Perfalgan (administered as 10 mg/1 mL) and 2 g of propacetamol (23). Other studies have established the current formulation of IV paracetamol to have comparable analgesic and antipyretic effects with the equivalent dosage of propacetamol (24-27). Because of ubiquitous IV access, the use of IV paracetamol is now widely practiced and seen as convenient with minimal latency to therapeutic effect. Cadence Pharmaceuticals introduced intravenous paracetamol in America in 2011.

IV paracetamol vs. oral and rectal formulations

A comparative study between the three common modes of administration found the IV formulation carries a faster time to peak plasma-drug concentrations (15 minutes after initiation of infusion) and a significantly higher peak plasma-paracetamol level (21). In contrast, oral paracetamol requires approximately 2 hours and rectal paracetamol at least 3 hours, depending on the placement of the suppository, to reach their respective peak plasma concentrations (21). These results correlate with the faster time to antipyresis in IV paracetamol compared to the oral formulation. Similarly, Levy proposed that the faster the time to complete absorption of an analgesic,

the longer-lasting the analgesic effect (28). This theory, however, has not been confirmed due to contradictory evidence from two other studies (29, 30). While there is not enough evidence to suggest superiority in terms of prolonged analgesia, several studies have questioned the ability of oral and rectal formulations to produce the desired plasma-paracetamol concentrations for effective analgesia (21, 31, 32). This issue is especially relevant to postoperative pain management studies. Sub-therapeutic plasma-drug concentrations with use of oral and rectal paracetamol, even at the recommended dosages, have been observed (21, 32). For this reason, IV paracetamol is also an attractive choice for postoperative analgesia.

Despite the above considerations, a clear disadvantage regarding the use of the IV formulation is the noticeable cost difference when compared to other methods of administration (*Figure 1*). In Australia, IV paracetamol costs $ 3.30 per 1000 mg, whereas two 500 mg oral tablets or rectal suppositories cost $ 0.026 and $ 1.24 respectively. Furthermore, this cost difference does not take into account the additional cost of an IV giving set as well as the inherent risks of IV administration. Current evidence has not determined whether IV paracetamol is more cost-effective than the other available formulations.

The haemodynamic effects of intravenous paracetamol

Most studies have focused on adverse effects associated with liver (33, 34) and renal function (35, 36), the impact of malnutrition and other rare occurring reactions such as thrombocytopaenia (37), anaphylaxis (38) or hypersensitivity and paracetamol-induced asthma (39). However, they are generally associated with chronic use and overdose, and are universal to paracetamol in general rather than the IV formulation in particular. The literature with respect to the acute side effects of IV paracetamol is limited; however these effects are clinically as important, if not more important, given how frequently the drug is administered intravenously to hospitalized patients.

Intravenous paracetamol-induced hypotension

Adequate maintenance of haemodynamic stability is often a determining factor before a patient can be discharged from the intensive care unit. Recent studies have linked the use of IV paracetamol with transient hypotension in the critically ill (8, 10-16). This may also be clinically relevant to surgical patients. Preoperative risk factors have long been used as an indicator of postoperative morbidity risk. However, there are only a few studies correlating the impact of intraoperative haemodynamic changes to poorer outcomes in the postoperative recovery. Tassoudis et al. found that an increased incidence of intraoperative hypotensive events was associated with morbidity and longer hospital stays (17). Hypotension, even if transient, should therefore be avoided. Given that IV paracetamol is ubiquitously used in the hospital setting further studies are required to explore its haemodynamic effects in this setting.

One of the first studies specifically examining the haemodynamic effects of the new ready-to-use formulation of IV paracetamol was published in 2010 (11).

This study showed a significant decrease in systolic blood pressure (SBP) with the use of IV paracetamol. In addition to the fall in SBP, nearly 35 % of the patients in the paracetamol group required intervention to stabilize blood pressure. Studies prior to this investigation, often reported insignificant differences in "vital signs", which included blood pressure measurements (25, 40, 41). However, these studies failed to report the time at which these measurements

were taken and may therefore have missed the critical window of time, where transient hypotension is said to occur. In 2009, Arici et al. published a study on the pre-emptive analgesic effects of IV paracetamol in total abdominal hysterectomy patients (40). A component of the study design was the evaluation of the intraoperative haemodynamic effects of IV paracetamol. However, a major limitation of this study was the authors' failure to specify how the haemodynamic effects were measured. Recently, Needleman investigated the safety of rapid infusion of IV paracetamol (12). In a retrospective chart review, IV paracetamol was found to cause statistically significant decreases in SBP, diastolic blood pressure (DBP) and mean arterial pressure (MAP). The study methodology required monitoring of these variables in 2 minute intervals following infusion and up until 5 minutes after infusion. The author did not determine if rapid infusion caused altered haemodynamics after this short period of monitoring. Boyle et al., however, provided evidence that IV paracetamol can cause reduced BP up to 60 minutes after infusion (10). It is unclear as to whether altering infusion times would reduce the onset of hypotension proposed in the current literature.

The studies available in the current literature (*Table 2*) tend to support the theory that IV paracetamol may have a propensity to induce hypotension. Compared to baseline values, administration of IV paracetamol resulted in significant decreases in either SBP or MAP in all studies (8, 10-16). However, the definition of hypotension differs between the papers, with values dependent on the opinion of the author. For instance, Boyle et al. determined a drop equal to and exceeding 15 % of the baseline blood pressure to be clinically significant (10), while de Maat et al. defined a decrease of at least 10 mmHg (11). Despite all of the above concerns, none of the studies were randomized, controlled or blinded, and all therefore lacked a placebo group. Thus, the level of evidence supporting the view that IV paracetamol induces hypotension is low and open to challenge. Additionally, most of the studies reported small participant numbers and three used vasopressors drugs to maintain blood pressure at a set level (10, 11, 13-15). This may have masked the magnitude of the apparent IV paracetamol-induced hypotension. Only one study considered measuring the serum concentration of IV paracetamol after infusion (11), but failed to comment on the relationship between paracetamol concentrations on haemodynamics. Future studies should seek to overcome these limitations to allow a correct understanding of the effects of IV paracetamol on blood pressure by evaluating cardiac output and systemic vascular resistance.

IV paracetamol-induced hypotension may be clinically important, especially in the setting of critical illness where it is most frequently reported (8, 10-16). Currently only two studies have investigated possible mechanisms for this trend. Boyle et al. suggested there might be a relationship between reduced skin blood flow and hypotension following administration of paracetamol in febrile patients (10). Additionally, IV paracetamol had little if any haemodynamic effect in the comparison afebrile healthy group. The authors concluded that the mechanism of hypotension could be caused by the antipyretic effect of IV paracetamol. However, IV paracetamol-induced hypotension has been produced in other studies where fever has not been specified or in afebrile patients, which contradicts this theory (11, 12, 16). Several limitations in the study design including lack of a control group, the use of a convenience sample of patients, and failure to adhere to one route of administration (results included findings from enteral and

Table 2 - *Summary of haemodynamic and intravenous paracetamol-specific papers in the current literature.*

Study	Drugs	Infusion time	Patient Group	Haemodynamic effects of IV paracetamol	Limitations
Picetti et al., 2014 (13)	1g IV paracetamol	15 minutes	ICU, acute brain injury with fever N = 32	Significant decrease in SBP, DBP and MAP for 60 minutes post infusion. Significant increase in number of patients receiving norepinephrine infusion post infusion.	Small number of participants Non-blinded Non-randomized No placebo group
Needleman, 2013 (12)	1g IV paracetamol	3.45 minutes*	Ambulatory surgical patients N = 100	Significant decrease in SBP, DBP and MAP post infusion. No clinical interventions were required at endpoint of study (5 minutes after infusion)	Short period in which haemodynamic monitoring occurred Non-blinded Non-randomized No placebo group Retrospective chart
Picettiet al., 2013 (14)	1g IV paracetamol	15 minutes	NICU, acute brain injury with fever N = 15	Significant decrease in MAP by 8.6 mmHg 120 minutes after infusion	Small number of participants Non-blinded Non-randomized No placebo group
Krajcova et al., 2013 (16)	1g IV paracetamol	10 minutes	Critically ill ICU N = 6	Significant decrease in MAP by 7% at 19 minutes after infusion > 15% decrease in MAP in 45% of measurements	Small number of participants Non-blinded Non-randomized No placebo group
Vera et al., 2012 (15)	1g IV paracetamol 2 g metamizol 0.5 g dexketoprofen	30 minutes	Critically ill with fever N = 150	Significant decrease in MAP over time. Max decrease by 8.5 + /-13.6 mmHg. Less hypotension in paracetamol compared to other groups	Use of vasoactive and vasodepressor drugs Non-randomized Non-blinded No placebo group Drug-patient bias (Drug selected by physician)
Duncan et al., 2012 (8)	1g IV paracetamol	Not specified	Critically ill N = unspecified	Significantly decreased SBP by 13 mmHg. Significantly decreased MAP by 8 mmHg 88% anecdotal reports by nurses of hypotension Senor ICU nurses claim hemodynamic stability for preference for enteral administration	Number of participants unspecified - determined the incidence of hypotension through anecdotal reports from doses of paracetamol. Not defined as randomized, blinded or having a placebo group. Reported the incidence of hypotension compared to that from enteral administration
de Maat et al., 2010 (11)	4x1g dose IV paracetamol (Perfalgan)	15 minutes	ICU and MCU Primarily postoperative patients N = 36	Significant decrease in SBP 15 minutes after infusion by 7mmHg and 30 minutes after infusion by 13mmHg compared to baseline. 33% patients had clinically relevant reduction in SBP 26% patients required intervention to correct blood pressure.	Small number of participants Use of vasopressor (noradrenalin) to maintain Non-blinded Non-randomized No placebo group
Boyle et al., 2010 (10)	Oral paracetamol tablets and Intravenous paracetamol Dose range: 500mg to 1g	Not specified	Critically ill with fever N = 29	Significant decrease in SBP 15, 30, 60 and 120 minutes after infusion vs. baseline. Clinically significant decrease in SBP (≥15%) in 59% patients within 60 minutes. Hypotension treated with vasoactive drug 33% required more vasoactive drug	Small number of participants Use of vasopressor Haemodynamic results include both IV and oral modes of paracetamol Biased patient selection (only ICU and cardiac surgery post-op patients) Non-randomized Non-blinded No placebo group

IV = intravenous; NICU = neonatal intensive care unit; ICU = intensive care unit; MCU = medium care unit; MAP = mean arterial pressure; SBP = systolic blood pressure. *Mean infusion time.

oral administrations) make it difficult to establish a causal link between these two observations. It would be clinically significant to establish whether these results can be replicated in afebrile, critically ill patients e.g. when paracetamol is indicated for the treatment of mild-moderate postoperative pain. Conversely, Krajcova et al., proposed that this type of drug-induced hypotension is the result of reduced cardiac output and systemic vascular resistance (16). However, this study was not able to identify the underlying cause of these findings and was limited to a small cohort of 6 participants.

Paracetamol-induced hypertension

In a study comparing effervescent para-cetamol to normal oral paracetamol tablets, clinicians were warned of the potential for effervescent paracetamol to cause a rise blood pressure (42).

The sodium content of effervescent paracetamol was implicated in this effect. Forman et al. conducted two studies that have established a relationship between the frequency of paracetamol use (oral tablets) and the incidence of hypertension in both male and female healthcare workers (43, 44).

A myriad of possible reasons for this effect were discussed, such as inhibition of vasodilatory prostaglandins and effects on endothelial function. However, the study failed to acknowledge the type of paracetamol tablet taken. This may be of considerable importance, because sodium content varies greatly. In fact, if participants in the study were taking Panadol Actifast (346 mg sodium per 2 tablets) at the manufacturer's recommended daily dosage, they would have ingested 1.38 g of sodium per day. It is therefore important to assess the effects of any additional compounds in all the formulations of paracetamol. This may be especially true for the IV formulations, considering its potential to cause hypotension.

Mannitol - an understudied excipient

Given that the therapeutic effect of IV propacetamol and IV paracetamol is comparable, it is imperative to identify any differences between the formulations in order to diagnose any possible cause for the observed haemodynamic changes. The currently used preparation of IV paracetamol is ready-to-use and available in solution due to the addition of stabilizing compounds. There are currently four major pharmaceutical companies that offer formulations of IV paracetamol (*Table 3*).

Of these, three companies utilize mannitol as the stabilizing compound. Pfizer is the only company that provides a mannitol-free infusion of IV paracetamol. Mannitol is secreted into the lumen of the nephron and causes a fluid shift resulting in increased urine production secondary to natriuresis. Due to osmotic forces, water is drawn from the peritubular blood and into the lumen of the nephron producing an increased volume of urine. Consequently, a reduction in blood volume may be expected to occur with the increased production of urine. Previously, mannitol was found to cause a redirection of systemic blood volume to the kidneys, which most likely exacerbates the subsequent decreased blood volume associated with its use (45). Hypovolaemia is a common cause of hypotension. The diuretic nature of mannitol, even in small doses, has been reported to cause episodes of transient hypotension (46). For the sake of consistency, studies that failed to observe haemodynamic changes but used (mannitol-free) IV propacetamol as a substitute for IV paracetamol should be considered separately in any analyses of the haemodynamic effects of IV paracetamol.

IV paracetamol (Actavis), Perfalgan (Bristol-Myers Squibb) and Ofirmev (Cadence Pharmaceuticals) contain close to 4 g of mannitol within a single 1g/100mL infusion of IV paracetamol solution (*Table 4*).

Table 3 - *Differences between each formulation of intravenous paracetamol sold by four major pharmaceutical companies (Trade names are listed in italics).*

	Perfalgan **Bristol-Myers Squibb**	***Ofirmev*** **Cadence Pharmaceuticals**	***IV Paracetamol*** **Actavis**	***IV Paracetamol*** **Pfizer**
Paracetamol (mg/100 mL)	1000	1000	1000	1000
Mannitol (mg)	3850	3850	3910	Nil
Cysteine hydrochloride monohydrate	✔	✔	✔	Nil
Dibasic dehydrate sodium phosphate	✔	✔	✔	Nil
Sodium hydroxide	✔	✔	✔	✔
Hydrochloric acid	✔	✔	✔	✔
Water for injections	✔	✔	✔	✔
Glucose	Nil	Nil	Nil	✔
Acetic acid	Nil	Nil	Nil	✔
Sodium acetate trihydrate	Nil	Nil	Nil	✔
Sodium citrate	Nil	Nil	Nil	✔

Table 4 - *The clinical uses of mannitol including dosage suggestions. Information from Osmitrol (Mannitol Infusion) Produced by Baxter Healthcare, Australia.*

Treatment	**Recommended Dosage**	**Equivalent Dosage/ 15 minutes**
Diuretic/Treatment of Oliguria	50-100 g over 24 hours	0.52-1.04 g
Prevention of Oliguria	10 g over 24 hours	0.625 g
Reduction of Intracranial Pressure	0.25-2 g/kg over 2-4 hours	2.19-8.75 g*
Reduction of Intraocular Pressure	0.25-2g/kg over 30-60 minutes	8.75-35.0 g*
Severe Oliguria/Excretion of Toxic Substances	Test dose: 14 g over 3 minutes	70 g**

Equivalent dosage per 15 minutes is estimated for comparison with IV paracetamol.
*estimated dosage for a 70 kg person; **exceeds dosage limit of 50 g/dose.

The manufacturer's recommendations for each of the respective companies suggest a maximum of 4 g of paracetamol administered daily for effective analgesic and antipyretic effects. This results in a recommended maximum daily dosage of 400 mL IV paracetamol, which corresponds to an infusion of an impressive dose of 15.4 g - 15.64 g of mannitol. Importantly, this must be considered in clinical situations that involve the routine use of mannitol, such as patients undergoing surgery to treat traumatic brain injury. Excessive use of mannitol can result in severe dehydration (47), volume changes (47), electrolyte imbalance due to free water losses (48), hypernatraemia (47), and hyperkaelemic acidosis in patients with diabetes mellitus (49). Only one of the haemodynamic studies listed the brand of IV paracetamol used. Maat et al. reported that IV Perfalgan can decrease systolic blood pressure between 15 to 30 minutes after the initiation of infusion (11).
Other studies suggest that IV paracetamol may continue to reduce blood pressure up to 120 minutes after infusion. However,

without knowing exactly which formulation was offered, the reasons for hypotension and whether such changes are due to mannitol or paracetamol remains unclear.

While the diuretic effect of mannitol is likely to contribute to hypotension, mannitol may be useful in other clinical settings. These are summarized with their corresponding dosages in *Table 4*. IV paracetamol is administered in an infusion over a 15 minute time period. When the recommended dosage of mannitol is calibrated over the prescribed infusion time of IV paracetamol, the concentration of mannitol in a single dose of IV paracetamol exceeds the therapeutic range for the treatment of diuresis and oliguria and is within the therapeutic range for the treatment of intraocular pressure. In the absence of uraemia, mannitol has a half-life of 127 minutes (50). With such a high dose of mannitol in IV paracetamol, it appears that a single infusion may effectively administer pharmacologically viable concentrations of two pharmaceuticals. Whether IV paracetamol can induce a reduction in intraocular pressure remains unsubstantiated. However, it is plausible that the mannitol found in the IV paracetamol formulations may cause enough of a diuretic effect to induce hypotension.

CONCLUSION

Intravenous paracetamol appears to be an effective analgesic and antipyretic. Recent data, however, suggest that its pharmacological value may be greater in some clinical settings compared to others. The IV preparation offers the ability to achieve therapeutic blood concentrations more readily and more reliably. However, there is limited data about the effects of IV paracetamol on haemodynamics. Importantly, emerging clinical data suggest that IV paracetamol has a propensity to cause hypotension in critically ill patients.

This issue may also be relevant to other patient subgroups, e.g. postoperative surgical patients, in whom maintenance of haemodynamic stability may be important to improved recovery. The quality of the studies linking paracetamol to hypotension, however, is low and the etiology of such putative hypotension has yet to be clarified. Nonetheless, if hypotension exists, it may be due to the separate effect of the stabilizing compound mannitol that is found in current formulation of IV paracetamol. This notion is supported by knowledge that mannitol is a known diuretic which, even in small quantities, can cause episodes of transient hypotension.

Moreover, in the majority of the formulations, 1 gram of IV paracetamol also contains nearly 4 g of mannitol, a clinically relevant dose. Further double-blind randomized controlled studies are required to identify whether IV paracetamol preparations do indeed induce hypotension and whether the mannitol in IV paracetamol is actually the agent responsible for the induction of hypotension.

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