

Intravenous paracetamol and intraocular pressure reduction: mannitol may also be involved

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Dear editor

I read, with great interest, the paper on the intraocular pressure-lowering properties of intravenous paracetamol (acetaminophen) recently published in this journal by van den Heever and Meyer.¹ The authors documented a decrease from baseline in mean intraocular pressure of 15.7% in a 6-hour time interval following intravenous paracetamol (1 g Perfalgan®, Bristol-Myers Squibb, New York, NY, USA) administration. This mean decrease was moderate but relevant when compared to, for example, topical timolol (–25.3%, single drop 0.5% timolol maleate) or oral acetazolamide (–23.1%, 250 mg). Although the authors provided potential relevant mechanistic arguments in support of a link between paracetamol administration and intraocular pressure through the endocannabinoid system, we would like to draw attention to the fact that – when intravenous paracetamol is administered – a relevant amount of mannitol is coadministered.

Clinicians and clinical researchers should be aware that drug formulations commonly contain excipient(s) besides the active compound(s). This is also true for Perfalgan® that contains ~3.9 g of mannitol (in 1 g paracetamol in a 100 mL vial).² I suggest that at least part of the effects observed may relate to the excipient, mannitol. Although recommendations do vary, mannitol doses of 0.25–2 g/kg over 30–60 minutes have been suggested to reduce intraocular pressure; while the paracetamol formulation results in coadministration of mannitol (3.9 g = 0.055 g/kg over 15 minutes). To further illustrate this, 12 g of intravenous mannitol resulted in a drop in intraocular pressures with a subsequent return to baseline by 2 hours in 38 eyes of 19 subjects.³

Understanding the mechanism(s) involved in the reduction in intraocular pressure matters and goes beyond academic reflections. First, not all currently marketed intravenous paracetamol formulations contain mannitol.² This means that the clinical message of the paper to consider recent exposure to intravenous paracetamol when interpreting ocular pressure measurement should be considered carefully until the mannitol effect has been disentangled from the paracetamol effect. Similarly, initiating acute or chronic exposure to paracetamol (either systemic through intravenous or oral, or topical) necessitates additional observations, adding another group exposed to similar amount of intravenous mannitol or comparing two paracetamol formulations containing one containing mannitol, the other without mannitol: “mannitol may matter.”

Disclosure

The author reports no conflicts of interest in this communication.

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Authors' reply

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Dear editor

We appreciate the comments received in response to our paper correctly highlighting the fact that not all intravenous paracetamol formulations contain the same excipients and that intravenous paracetamol has also manifested other unintended systemic side effects. An example of this is apparent systemic hypotension.^{1,2} Whether these unintended effects result from pharmacological (drug or excipients) or nonpharmacological (volume addition or excipients) factors is not yet clear. Further studies comparing different formulations of intravenous paracetamol will assist in quantifying the relative contribution of the following components of intravenous paracetamol to possible change in intraocular pressure (IOP): rapid addition of intravascular volume, paracetamol as a drug, and the excipients in the solution.²⁻⁴

Given the known inconsistency of the dose-response curve of mannitol, purely theoretical prediction of any ocular hypotensive effect at the quantities contained in Perfalgan® (3.85 g and 300 mOsmol/kg) would probably not be helpful without clinical testing.⁵ This should form the primary objective in a follow-up study.

What we do know is that paracetamol has IOP-lowering properties and numerous papers show that paracetamol interacts with the endocannabinoid system.⁶⁻⁹ Unpublished data from our laboratory show that topical paracetamol has IOP-lowering properties in New Zealand White rabbits.

The aim of our study however was to attempt to answer the following question in clinical ophthalmology: Is there a change in IOP after intravenous administration of paracetamol (in our case, Perfalgan®)? Although an ocular hypotensive effect might support the endocannabinoid mechanism of action of paracetamol claimed by Högestätt et al⁹ and Ottani et al,⁸ this was not the conclusion of our study. Our findings could only conclude that clinicians interpret IOP measurements taken within 6 hours after the administration of intravenous paracetamol with caution.

Disclosure

The authors report no conflicts of interest in this communication.

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