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Review article

What we don't know about paracetamol in children

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Introduction

Il faut cultiver son jardin, Voltaire.

The introduction of FDA regulations governing marketing of new drugs ensures children will cease to endure the role of therapeutic orphans. However, anaesthetists involved in the care of children have always sought to define the pharmacokinetics and pharmacodynamics of drugs used in their practice. Unfortunately, these studies have usually only been undertaken for the newer or 'glamour' drugs, partly because of their ability to attract pharmaceutical funding for research. Common or 'garden' drugs such as paracetamol have, until recently, been ignored.

Paracetamol has been used in clinical practice for over one hundred years. Acetanilid, the parent compound of paracetamol, was introduced in 1886. Toxicity related problems with acetanilid lead to the introduction of paracetamol (acetaminophen, N-acetyl-p-amino-phenol) by von Mering in 1893. The popularity of paracetamol over the nonsteroidal anti-inflammatory agents ascended after the reported association between Reye's syndrome and aspirin in the 1980s (1). The drug is well tolerated, lacks many of the side effects of aspirin, is available without prescription and is widely used in the management of children with pain or fever.

Pharmacodynamics

a) Antipyresis

Paracetamol is commonly prescribed to reduce fever. Fever under 41°C is unlikely to cause harm. Temperatures above this caused by heat stroke or cerebral damage are unlikely to respond to such a simple measure. In the presence of cardiac or respiratory disease the reduction of temperature may help reduce oxygen consumption, carbon dioxide production and cardiac output while helping the child to settle. Paracetamol is used to reduce the symptoms caused by mild acute infections in children. In such viral infections paracetamol results in only a modest improvement in activity and alertness. Mood, comfort, appetite and fluid intake were not improved compared to controls (2,3). It is assumed that the fever associated with infections causes discomfort. This premise has not been substantiated. Indeed treatment of fever may impair antibody production (4) and delays parasite clearance time in children suffering malaria (5).

Paracetamol is reported to be an effective antipyretic at serum levels of 10–20 $mg \cdot l^{-1}$ (6,7). This relationship between serum concentration and temperature is loosely defined. Several papers have documented time delays of 1–2 h between maximum plasma concentrations and maximum temperature reduction (6,8). It is logical that these time delays should occur, given that the effect site is the hypothalamus which must induce physiological body changes to cause temperature reduction. The population pharmacodynamic parameters, however, have not been defined.

Pharmacodynamics of many biological systems can be defined using a sigmoid Emax model (9).

$$\text{Effect} = E0 + (\text{Emax} * Ce^N)/(EC50^N + Ce^N)$$

where E0 is the baseline response, Emax is the maximum effect change, Ce is the concentration in

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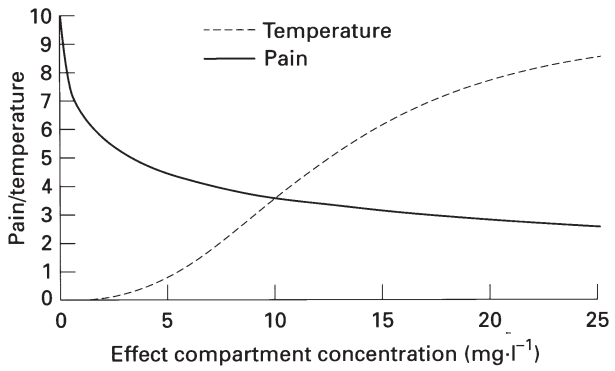

Figure 1
Pharmacodynamics of paracetamol. Temperature reduction is in °F. Pain Score ranges from 0 (no pain) to 10 (worst pain imaginable). The slope of the temperature response curve is steeper in the central portion than that for analgesia.

the effect compartment, EC50 is the concentration producing 50% Emax, and N is the Hill coefficient defining the steepness of the concentration-response curve. This model predicts no effect when no drug is present and is also capable of predicting a maximum effect the drug can achieve. Despite paracetamol use for over 100 years, we do not know the maximum temperature reduction (Emax) possible. Nor do we know the influence of covariates such as age or disease process on pharmacodynamics. The equilibration half-time (Teq), which is the link describing the relationship between the central compartment and the effect compartment, is unknown. We are left with the loose understanding that temperature reduction occurs when concentrations are in the range 10–20 mg·l^{-1} (6,7).

Studies documenting concentration–temperature reduction hysteresis loops usually report naïve pooled data (6). While it is possible to apply pharmacokinetic-pharmacodynamic (PK–PD) modelling techniques to such data, it is not possible to distinguish variability within individuals and between individuals. The model is 'washed out' by the data. A paracetamol pharmacodynamic concentration-temperature reduction model for fever has been described in children using pooled data (Figure 1) (10). The shape of this curve is steep in its central portion (Hill coefficient 2.65). A temperature reduction of 3.5°F is predicted at a target concentration of 10 mg·l^{-1}. At 20 mg·l^{-1}, we would expect a temperature reduction of 7.6°F.

b) Analgesia

Paracetamol is thought to have an analgesic effect on NMDA receptors in the spinal cord (11,12). It is assumed that analgesia occurs in a similar plasma paracetamol concentration range to that required for antipyresis (13). This is unproven. The analgesic effect of paracetamol is thought to be directly related to its plasma concentration (14) because of its high lipid solubility and low protein binding in this concentration range (15). Certainly, Granados-Soto *et al*. (16) have demonstrated a direct relationship between plasma concentration of acetaminophen and its analgesic effect in rats using a sigmoid Emax model with a Hill coefficient of 2.13 and an EC50 of 124 mg·l^{-1}.

The pharmacodynamics of paracetamol analgesia have not been adequately described in humans. Postoperative use of paracetamol in combination with opioids is reported to reduce opioid requirements by 16–26% after elective gynaecological laparotomies (17). Adult human studies performed in volunteers demonstrated 0.5 g and 1 g immediate release paracetamol had analgesic effect superior to placebo for one to five h, but no difference in analgesic effect was noted between doses (18). The pain threshold was significantly elevated compared to placebo one and two h after paracetamol ingestion. The addition of codeine 60 mg to paracetamol 1 g was superior to placebo one to six h after medication (19). These studies also demonstrated a delay between maximum analgesia and peak plasma paracetamol concentrations of an hour. The relationship between concentration and effect cannot be as straightforward and simple as that described in the rat model because of these time delays.

Paediatric studies using paracetamol 10 mg·kg^{-1} *po* have shown no more analgesic effect than placebo in children undergoing myringotomy (20) or suffering symptoms of tonsillitis and pharyngitis (21). Paracetamol 15 mg·kg^{-1} *po* given to unanaesthetized neonates undergoing circumcision was found not to ameliorate either intraoperative or immediate postoperative pain (22). Several recent papers (23,24) have investigated the analgesic efficacy of paracetamol alone after tonsillectomy in children. These studies have demonstrated the need for supplemental analgesia in the postoperative period. Rusy (22) demonstrated low or even undetectable serum

paracetamol concentrations in the first 40 min after surgery after 30–35 $mg \cdot kg^{-1}$ *pr* intraoperatively. Mather (24) showed a need to supplement rectal paracetamol 20 $mg \cdot kg^{-1}$ with a nonsteroidal anti-inflammatory agent to achieve satisfactory analgesia. The intravenous prodrug of paracetamol (propacetamol) 30 $mg \cdot kg^{-1}$ has been shown to give superior analgesia compared to placebo after orthopaedic surgery (25).

Most studies investigating paracetamol analgesia have not included plasma paracetamol concentrations as part of their analyses (20,21,24–27). The few studies that have measured concentrations report them to be below 10 $mg \cdot l^{-1}$ after either the oral formulation 10–15 $mg \cdot kg^{-1}$ given four hourly (28) or a single rectal dose of 20 $mg \cdot kg^{-1}$ (13). These poor results may either reflect inadequate dosing and/or slow absorption of rectal paracetamol. Adequate analgesia in children undergoing tonsillectomy has been described using acetaminophen 40 $mg \cdot kg^{-1}$ *po* preoperatively (29). In that study children were given either rectal or oral paracetamol in order to achieve a spectrum of paracetamol concentrations and the analgesic assessment made at one fixed point in time. Fifty percent of children had satisfactory analgesia at a concentration of 17 $mg \cdot l^{-1}$ (30). We would expect equivalent effect compartment concentrations to be lower because of delayed onset of effects.

Many clinical studies in which paracetamol is compared to another analgesic after a surgical insult are destined to either fail to show a difference between the two analgesic treatments or to have inadequate power because pain score reporting methods, the pain stimulus and pharmacokinetic parameters all have large variability.

Development of indirect measures of pain intensity (e.g. measurement of transient changes in blood flow by laser Doppler) will help decrease variability of effect measures. However pharmacokinetic variability remains. Prescott (31), in a study of 43 adult convalescent patients, reported an 80 fold range in concentrations one hour after three 500 mg tablets. Such variability will have impact on effect. Pharmacokinetic variability appears to have considerable impact on response rates for fever control (32). Similar considerations must certainly apply for analgesia and should be considered in the design and interpretation of clinical trials.

The pharmacodynamics of paracetamol analgesia in children, or adults for that matter, have not been adequately addressed. The shape of the concentration-response curve may be quite different from that describing temperature reduction. A Hill coefficient of only 0.5 has been postulated to describe the analgesic response (33). Such a curve is shallower in its central portion, but steeper at low concentrations when compared to that describing fever control (Figure 1). Doubling the effect compartment concentration from 10 to 20 $mg \cdot 1^{-1}$ will result in only a minor reduction of pain.

The estimation of population pharmacokinetic-pharmacodynamic parameters is difficult due to the complexity of analgesic clinical trials and requires advanced modelling techniques such as nonlinear mixed effect models (NONMEM) (34). Placebo effect can contribute significant analgesia. Twenty-four percent of children received adequate analgesia after tonsillectomy despite no detectable plasma paracetamol (30). However, the continuing use of placebo controls has been strongly argued against in the literature (35). Pain intensity may change over the study period. Patients who receive rescue medication and are withdrawn from a study introduce additional bias as the remaining study patients are those who do not have such severe pain; the reason for their reduced analgesia may not be solely pharmaceutical (34,36). Pain relief measurements are nonrandomly censored. Pain scores are often treated as continuous rather than categorical data. In addition to these difficulties, pharmacodynamics may change with age. Neonates, for example, may have altered pharmacodynamics when compared with older children!

Regardless of age-related pharmacodynamic changes, the drug must be administered 1–2 h before a surgical insult if an analgesic effect is to be achieved.

Pharmacokinetics

a) General

Pharmacokinetic studies in children are often limited by the small number of blood samples which can be taken from an individual child. Data are often presented as an average maximum concentration at an average maximum time (37,38). These confounded parameters (and the derived estimate of elimination

half-life) are highly dependent on sampling times. Pooled data may give an erroneous impression of results (39). For example, Birmingham *et al*. (40) demonstrated that average peak concentrations of 5–6 $mg \cdot l^{-1}$ occurred at 240–300 min after rectal paracetamol, but the maximum mean concentration was 8.8 (SD 3.4) $mg \cdot l^{-1}$ and the time to maximum mean concentration was 288 (SD 126) min.

The measurement of urinary paracetamol and its metabolites has been used in children and neonates. Reasonable pharmacokinetic estimates have been made but the method is dependent on complete collection of all urine. Pharmacokinetic computer programs have simplified the use of nonlinear regression using iterative techniques. Simple two stage population estimates for paracetamol have been reported. However, true population pharmacokinetic estimates have, until recently (10,40), not been used.

The effects of altered physiology such as fever (8), anaesthesia (41), or hepatic dysfunction (42) on pharmacokinetic parameters have received little attention, but appear to have minimal impact.

b) The impact of size

Size has considerable impact on our interpretation of age-related pharmacokinetic changes. Size must be disentangled from age in order to understand developmental changes in the young. Clearance is a nonlinear function of size. The allometric $\frac{3}{4}$ power model is a more accurate predictor of size than the per kilogram model for metabolic processes (43,44). This model can be expressed as

$$X_i = X_{std} * (W_i / W_{std})^{PWR}$$

where X_i is the parameter in the ith individual, W_i is the weight in the ith individual and X_{std} is the parameter in an individual with a weight W_{std}. The PWR parameter was 0.75 for clearance, 1 for distribution volumes and 0.25 for half-lives (45–47). In humans underprediction of clearance of more than 10% occurs at body weights less than 47 kg when the per kg model is used (44). Inappropriate size models for young children have led to misconceptions such as the enhanced capacity of children to metabolize drugs. This misconception has been demonstrated for the clearance of theophylline (48) and analgesics in children (49). The model assists in the ability to predict the parameters in a given species, including humans, based on values found for other mammalian species (47).

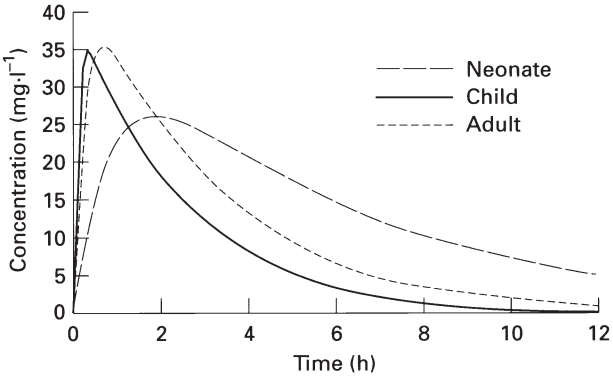

Figure 2
Time-concentration profiles for paracetamol 40 $mg \cdot kg^{-1}$ given orally. Parameters used were adult (84) CL/Foral 0.3 $l \cdot h^{-1} \cdot kg^{-1}$, Vd/Foral 0.9 $l \cdot kg^{-1}$, Tabs 0.17 h; child (8) CL/Foral 0.43 $l \cdot h^{-1} \cdot kg^{-1}$, Vd/Foral 1.03 $l \cdot kg^{-1}$, Tabs 0.045 h, Tlag 0.07 h; neonate (52) CL/Foral 6.5 $l \cdot h^{-1} \cdot 70\ kg^{-1}$, Vd/Foral 76 $l \cdot 70\ kg^{-1}$, Tabs 0.58 h.

c) Absorption

Paracetamol is a weak acid with a high pKa. In the alkaline medium of the duodenum paracetamol is nonionised. Consequently, absorption of the nonionised form in the duodenum is rapid. Brown *et al*. (50) have reported rapid absorption (Tabs 2.7, SE 1.2 min; Tlag 4.2, SE 0.4 min) parameters in febrile children (Figure 2). If these data can be reproduced in children who have been subjected to a preoperative fast, then we would expect almost complete transit through the pylorus after 30 min. However, the effect of preoperative paracetamol elixir on gastric contents has not been investigated.

Rectal paracetamol is widely used in children presenting for surgical procedures because of gastrointestinal dysfunction or NPO policies. Several models have been used to describe rectal absorption. Birmingham *et al*. (40) have reported a first order input model with a zero order dissolution time to describe absorption characteristics of acetaminophen suspended in a hydrogenated vegetable oil base. A first order input model with a lag time has been used to describe absorption from glycogelatin capsules containing an acetaminophen slurry (51). Regardless of the model or the suppository type, absorption is

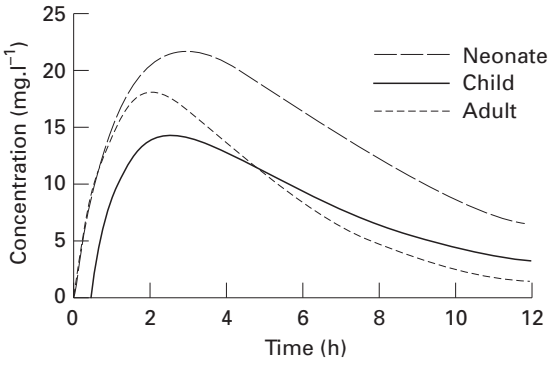

Figure 3
Time-concentration profiles for paracetamol 40 mg·kg^{-1} given rectally. Parameters used were adult (84) 0.3 l·h^{-1}·kg^{-1}, Vd/Foral 0.9 l·kg^{-1}, Tabs 1 h, Frectal/oral 0.8 (85); child (51) CL/Frectal 0.35 l·h^{-1}·kg^{-1}, Vd/Frectal 1.9 l·kg^{-1}, Tabs 0.713 h, Tlag 0.44 h, Frectal/oral 0.52 (54); neonate (52) CL/Frectal 6.5 l·h^{-1}·70 kg^{-1}, Vd/Frectal 76 l·h^{-1}·70 kg^{-1}, Tabs 1.22 h, Frectal/oral 1. Peak concentrations in the neonate are higher because of greater relative bioavailability. The relative bioavailability and absorption half time (Tabs) both have high variability in all age groups. Peak concentrations are delayed when compared to oral formulations.

slow and variability high. Peak concentrations are not reached for 2–4 h (Figure 3) in premature neonates, infants and children (38,40,51,52).

d) Bioavailability

Paracetamol has low first pass metabolism and the hepatic extraction ratio is 0.11–0.37 in adults (53). The relative bioavailability of rectal compared with oral acetaminophen formulations (Frectal/oral) has been reported as 0.52 (range 0.24–0.98) (54) and even as low as 0.3 (55) The relative bioavailability may be as high as 1 in neonates (52) where it is possible suppository insertion height may result in a different rectal venous drainage pattern. The impact of the rectal venous drainage pattern is questionable, given the degree of rectal venous anastomotic channels, slow absorption times and natural attrition from the rectum.

e) Clearance

Pharmacokinetic changes with age have received scant attention. We know that the manner in which the liver metabolizes paracetamol changes with age. There is reversal of the usual adult ratio of 2:1 glucuronide to sulphate conjugates of paracetamol in young children. This pattern reverts to adult pattern at the age of 12 years (56). However, we have few data concerning clearance in the very young or the speed of enzyme maturation.

Autret *et al*. (57), using an intravenous prodrug of acetaminophen, report a clearance (CL) of 4.5 l·h^{-1}·70 kg^{-1} in neonates, rising to 14 l·h^{-1}·70 kg^{-1} out of the neonatal period (if a mean weight of 7 kg is assumed for infants). A similar estimate (CL/Foral) of 6.5 l·h^{-1}·70 kg^{-1} has been reported in neonates from an intensive care unit (52), rising to 10 l·h^{-1}·70 kg^{-1} in children (10). This estimate in children is similar to that determined after a rectal preparation (CL/Frectal 18 l·h^{-1}·70 kg^{-1}, CV 42%) (51), given a relative bioavailability of 0.52. These estimates are at the lower range of those reported for adults (CL/Foral 12–21 l·h^{-1}) (58).

f) Volume of distribution

The distribution volumes (Vd/Foral) of paracetamol in mammals, including man, are similar (0.7–1.0 l·kg^{-1}; 56–70 l·70 kg^{-1}) (58), as we would expect from the allometric size model with a power function of 1. The Vd/Foral appears to be similar even in neonates (76 l·70 kg^{-1}, SD 29) (52). The volume of distribution is an important determinant of any loading dose. We would expect the oral loading dose to be similar in all age groups (Figure 1). The rectal loading dose may vary with age depending on relative bioavailability (Frecta/oral) and absorption parameters (Figure 2).

Dosing schedules

a) Children

Paracetamol is commonly given in a dose of 10–15 mg·kg^{-1} four hourly (59) orally and 15–20 mg·kg^{-1} four hourly rectally (60). Nahata and Powel (61) have demonstrated that 24–30 mg·kg^{-1} eight hourly *po* gives levels in the antipyretic range. These data are supported by Sanderson *et al*. (62). Perioperative plasma concentrations were measured at 24 h after a scheduled dosing regimen of 20 mg·kg^{-1} six hourly in children. The mean peak

concentration was 16 mg·l^{-1} (range 6.7–21 mg·l^{-1}) and the mean trough 7.6 mg·l^{-1} (range 3.2–12.5 mg·l^{-1}).

Rectal absorption is slower and more variable than oral. Paracetamol 15–20 mg·kg^{-1} has been shown to give plasma concentrations which are below antipyretic concentrations (13). Concentration in the range 10–20 mg·l^{-1} can be achieved with rectal loading doses of 35–45 mg·kg^{-1} (40,51,63).

Shann (64) has suggested a loading dose of 20 mg·kg^{-1} *po* paracetamol with maintenance doses of 15 mg·kg^{-1} 4 hourly *po*. When the drug is administered rectally a 40 mg·kg^{-1} loading dose should be followed by 20 mg·kg^{-1} after six h using a six hourly dosing interval in order to keep below the 90 mg·day^{-1}·kg^{-1} recommendations. Alternatively 30 mg·kg^{-1} may be given 8 hourly. These schedules are based on avoiding potential toxicity rather than PK-PD considerations. Although the bioavailability of rectal formulations are below those given orally, the upper dose limit for rectal formulations is the same as oral as the medication is often charted either *pr* or *po* interchangeably and some children will have a high relative bioavailability (Frectal/oral). The problem is that many children will have inadequate con centrations when paracetamol is administered rectally for analgesia using the 90 mg·day^{-1}·kg^{-1} regimen (32). In the perioperative period, however, it may be possible to use a combination of preoperative oral and intraoperative rectal paracetamol to maintain a target concentration into the recovery period.

b) Neonates

Many practitioners are wary of prescribing paracetamol to neonates because neonates have an immaturity of hepatic glucuronide processes. Neonates are capable of forming the reactive intermediate that causes hepatocellular damage (65, 66), despite a comparatively low level of cytochrome P450 system (67). However, the rate constant for the sulphation metabolic pathway is larger in neonates than in adults and is the most important route of metabolism (56). This pathway is not related to serum bilirubin concentrations (68). Single doses of 12–15 mg·kg^{-1} *po* achieve therapeutic serum concentrations (37,68).

Autret *et al*. (57), using an intravenous prodrug of paracetamol (propacetamol chlorhydrate) estimate a 30 mg·day^{-1}·kg^{-1} dose will give satisfactory plasma concentrations if given enterally. This extrapolation does not take into account the slower absorption half lives of rectal and oral formulations. Rectally a loading dose of 40 mg·kg^{-1} followed by 30 mg·kg^{-1} 12 hourly or orally a loading dose of 30 mg·kg^{-1} followed by 20 mg·kg^{-1} 8 hourly will achieve concentrations of 10–20 mg·l^{-1} (52). However, the problem of cumulative toxicity with repeated dosing has not been addressed in neonates.

c) Infants

Infants have developed similar clearances of paracetamol to older children by the age of one year (10). Dosage regimes recommended err on the cautious side (60 mg·day^{-1}·kg^{-1}) (8) again reflecting the lack of well conducted pharmacokinetic studies.

Toxicity

a) Chronic use

There has been a reticence among practitioners to prescribe higher doses of paracetamol (69). Paracetamol overdose results in increased production of highly reactive electrophilic arylating metabolites by the hepatic cytochrome P-450-dependent mixed function oxidase enzyme system (70). These metabolites bind to intracellular hepatic macromolecules to produce cell necrosis and damage. Paracetamol may accumulate in paediatric patients after repeated therapautic doses (71). There is adult evidence of glutathione depletion in volunteers given doses of 0.5 g and 3 g paracetamol separated by four to ten days (72). Penna & Buchanen (73) reported seven deaths and 11 cases of hepatotoxicity associated with paracetamol in children. Mortality due to hepatoxicity was associated with doses greater than 300 mg·day^{-1}·kg^{-1} for one to six days. Survival was usually seen in those children suffering hepatotoxicity due to paracetamol greater than 150 mg·day^{-1}·kg^{-1} for two to eight days. Current guidelines (59,64) recommend that doses should not exceed 90 mg·day^{-1}·kg^{-1}, although a recent review suggests an even more conservative dose of 75 mg·day^{-1}·kg^{-1} (74).

The propensity for toxicity is increased by significant hepatic and renal disease, malnutrition

Table 1
Pharmacokinetic parameters standardized to a 70 kg person

Age	*CL/Foral*	*Vd/Foral*	*T1/2*
	($l \cdot h^{-1} \cdot 70\ kg^{-1}$)	($l \cdot 70\ kg^{-1}$)	(h)
Neonate (52)	6.5 (CV 52%)	76 (CV 38%)	9.6 (CV 48%)
Child (10)	10 (CV 56%)	60 (CV 21%)	4.2 (CV 56%)
Adult (85)	12–21	56–70	2–3

CL/Foral = total body clearance after oral administration; Vd/Foral = volume of distribution after oral administration; T1/2 = elimination half life standardized to a 70 kg person.

and dehydration. Medications which induce the hepatic P450 system (e.g. phenobarbitone, phenytoin, rifampicin) may also increase the risk of hepatotoxicity.

b) Single dose

The plasma concentration associated with toxicity after a single dose of paracetamol is extrapolated from adult data. The Rumack–Matthew (75) acetaminophen toxicity normogram is widely used to guide management of paracetamol overdose in adults and children. This normogram was derived from a study by Prescott *et al*. (76) of 30 adult patients who ingested an overdose of paracetamol. In poisoned patients with similar initial concentrations, the half-life in those without liver damage was 2.9 (SE 0.3) h and in those with liver damage 7.6 (SE 0.8) h. Paracetamol concentrations of more than $300\ mg \cdot l^{-1}$ at four h were always associated with severe hepatic lesions, but none were observed in patients with concentrations less than $150\ mg \cdot l^{-1}$. The half-life was less than four h in all patients without liver damage.

Clearance is a nonlinear function of weight. Dose is usually expressed as a linear function of weight. As a consequence younger children require larger doses than older children and adults to achieve similar concentrations at four h. This has been demonstrated in animals. Young rats have a higher median lethal dose than older rats (77). More drug is required to produce a hepatotoxic reaction (77).

Young children under the age of six years are thought to be less susceptible to toxicity than older children and adults (78). It is estimated that less than 5% of children under six years with paracetamol concentrations above the Rumack–Matthew treatment line will develop transient hepatic abnormalities (76). This may, in part, be attributable to the shorter half-lives seen in children. In addition, young rats have been reported to have an increase in the rate of glutathione synthesis when compared to older rats, as well as a capacity to increase glutathione levels after depletion (79). Glutathione may then provide increased detoxification. These data were not standardized to an allometric size model, nor is the applicability to children certain. These arguments are, however, supported by data from Bond *et al*. (80), who recommend determination of plasma concentrations in children aged under six years, only if they have ingested more than $200\ mg \cdot kg^{-1}$.

Adults may be more susceptible to hepatic damage due to its complex interaction with alcohol. This interaction has recently been reviewed by Slattery *et al*. (81). The toxic metabolite of acetaminophen, N-acetyl-p-benzoquinone imine (NAPQI) is formed by the cytochrome P450s CYP2E1, 1A2 and 3A4 (81). CYP2E1 is the most significant of these. Alcohol induces and is a substrate for CYP2E1. If, after enzme induction by alcohol, acetaminophen is ingested without alcohol, then increased formation of NAPQI occurs (81). Lower amounts of P-450 cytochrome oxidase system metabolites have been reported in children (81). Under-reporting of dosage during parasuicide attempts (83) and absorption variability due to other drugs (e.g. dextropropoxyphene (84)) or acetaminophen formulation also contribute to the increased toxocity seen in adults.

Conclusions

Paracetamol has been used as an antipyretic analgesic for over 100 years. Much has been learned about its pharmacokinetics in recent years. However, there are still huge gaps in our knowledge about this common drug. Paracetamol pharmacokinetics in the very young have yet to be elucidated. The problem of cumulative toxicity with repeated dosing has not been addressed in this younger age group. We know less about paracetamol pharmacodynamics at any age than we do about the newer synthetic opioids. Much work remains to be done defining population PK-PD relationships. The target concentration of paracetamol is undefined. Studies using the intravenous prodrug of paracetamol (propacetamol)

may simplify these PK-PD studies by allowing greater accuracy of dose and removing drug absorption variability from pharmacokinetics; development of indirect measures of pain intensity may refine pharmacodynamic data. Future investigations must also include an appropriate size model in order to disentangle developmental changes in the young from those changes related to size alone.

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