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Review Article

Recommended use of morphine in neonates, infants and children based on a literature review: Part 1—Pharmacokinetics

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Summary

The English language literature has been reviewed in order to evaluate the present knowledge on morphine's metabolism and pharmacokinetics in children. The majority of preterm neonates are capable of glucuronidating morphine, but birth weight, gestational and postnatal age influence the glucuronidation capability. Term neonates, infants, and children are able to produce morphine glucuronides. For the reported pharmacokinetics parameters a meta-analysis was made; volume of distribution, estimated to be 2.8 ± 2.6 $l \cdot kg^{-1}$, seems to be regardless of age, while half-life and clearance were found to be related to age. Half-life was estimated to be 9.0 ± 3.4 h in pre-term neonates, 6.5 ± 2.8 h in term neonates aged 0–57 days, and 2.0 ± 1.8 h for infants and children aged 11 days to 15 years. Clearance was estimated to be 2.2 ± 0.7 $ml \cdot min^{-1} \cdot kg^{-1}$ for preterm neonates, 8.1 ± 3.2 $ml \cdot min^{-1} \cdot kg^{-1}$ in term neonates aged 0–57 days, and 23.6 ± 8.5 $ml \cdot min^{-1} \cdot kg^{-1}$ in infants and children more than 11 days old.

Keywords: morphine, metabolism; pharmacokinetics; children; review

Introduction

Different studies have found that children postoperatively did not get analgesic treatment to the same extent as adults, and that children often experienced postoperative pain (1–6). The reasons for the undertreatment of pain in children were partly due to the persistence of old myths such as 'small infants have an immature nervous system and are unable to feel pain' or 'children do not remember pain and therefore do not experience pain in the same way as adults do, consequently they do not need analgesic treatment to the same extent as adults do'. These beliefs have been proven wrong (7–9). Other misconceptions are, that it is unsafe to administer opioids to children, and that children often suffer respiratory depression following administration of morphine. The aim of this review is to evaluate the present knowledge of the metabolism and pharmacokinetics of morphine in neonates, infants and children, and in this way contribute to the basis on

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Table 1
The percentage of the number of preterm neonates studied from whom M3G and M6G have been detected from either plasma or urine samples.

Author	*Sample (n)*	*M3G detected (%)*	*M6G detected (%)*
Choonara *et al.* (12)	9 SS*	100	56
Bhat *et al.* (16)	13 SD†	38	23
Chay, Duffy, Walker (17)	4 SS	100	0
Hartley *et al.* (18)	10 SS	100	100
Hartley *et al.* (19)	23 SS	100	100

* SS = sampling in steady state; † SD = sampling after single dose administration.
The neonates were born at 24–37 gestational week, weighed 580–2260 g and were 0–12 postnatal days old.

which clinical decisions on morphine usage in children are made. The findings of this review are presented in two articles; part one discusses the pharmacokinetics of morphine, and part two the clinical use of morphine. English language literature has been identified by Medline searches, and additional publications from cited references. To obtain the most accurate data only original articles have been included, hence published abstracts are omitted.

Metabolism and excretion

Glucuronidation is the main metabolic route of morphine with morphine-3-glucuronide, (M3G), and morphine-6-glucuronide (M6G) being the most abundant metabolites. The glucuronidation process is mainly located in the liver. The formed glucuronides are excreted by the kidneys, and impaired renal function leads to accumulation of M3G and M6G (10,11).

It has been suggested that the glucuronidation pathway is present, but immature at birth and continues to develop after the neonatal period, and that the M3G and M6G pathways develop in a parallel manner (12,13). It is well established that term neonates, infants and children are capable of metabolizing morphine to M3G and M6G (10,12,14, 15). In preterm neonates the development of the glucuronidation pathway has been studied by several groups (12,16–19) who have reported diverging results concerning the presence of M3G and M6G (Table 1). In four of the studies M3G was detected in either plasma or urine samples from all the neonates (12,17–19) and Chay *et al*. detected M6G in only a part of the neonates producing M3G; possibly due to the sensitivity of the assay (12,17). Only Bhat *et al*. had a group of neonates, 46%, from whom it was impossible to detect either M3G or M6G (16). This could be because they studied morphine metabolism after a single dose of morphine while the other groups used steady-state measurements. Another diverging factor is the study population as Bhat *et al*. studied neonates that were younger and lighter than those of the other studies. It is controversial whether gestational age, birth weight and postnatal age influence the glucuronidation capacity (16,17,19), but gestational age and birth weight influence the maturity and the size of the liver. Hartley *et al*. found a weak, but significant correlation between glucuronidation capability and gestational age (19).

Another metabolic pathway of morphine is sulphation; this pathway has only been briefly studied. Morphine has been found to be conjugated to morphine-3-sulphate in premature neonates and children, but the available findings signify that sulphation is a minor metabolic pathway of morphine and that sulphation is diminished after the neonatal period (21). Preliminary results have supported these findings, and indicated that the glucuronide/ sulphate ratio in infants is 1.5 (13,22). Unfortunately no follow-up investigations have been reported.

The ratio of M6G/M3G increases with decreasing birth weight (13) indicating that the formation of the analgesic active metabolite, M6G, increases with decreasing birth weight. This can, however, probably not explain the longer duration of action after a single dose of morphine in neonates, since the ratios of M3G/morphine and M6G/morphine in both plasma and urine are lower in neonates than in children (12, 13), signifying that neonates have a lower metabolic capacity than older children. Thus the longer effect of a single dose of morphine seen in neonates can

most probably be ascribed to the lower metabolic capacity and thereby the lower elimination rate of morphine in neonates.

It seems that renal excretion of unchanged morphine is more profound in neonates than in adults. In adults renal clearance accounts for approximately 10% of the total body clearance (25), while in preterm infants 3–15% of a morphine dose was excreted as unchanged morphine (16) and in term neonates 16–80% of the infused dose (24). Estimated renal clearance accounts for 19% of the total body clearance in term neonates younger than three months, and for 13% in older infants (13). As renal function develops rapidly during the first days of life due to change from maternal to neonatal renal function, postnatal age may be important for the excretion of unchanged morphine and metabolites.

Pharmacokinetic parameters

A number of groups have studied the pharmacokinetic behaviour of morphine after administration in neonates, infants and children. The pharmacokinetic parameters of morphine investigated more extensively include distribution, half-life and clearance. The studies identified are listed chronologically according to gestational and postnatal age in Table 2. All studies have been given a reference number, that are used in the Figures 1, 2 and 3 showing the obtained mean values for volume of distribution, half-life and clearance. If a study has not included the actual pharmacokinetic parameter, this has been indicated with a mark at the x-axis. Studies including only one or two children are not included. To evaluate a possible correlation between studies, meta-analysis based on reported mean values, standard deviations, and number of children studied was performed. The obtained pooled estimates for volume of distribution, half-life and clearance are listed in Table 3.

Distribution

The distribution of morphine has been described by a bi-exponential function composed of a rapid initial distribution phase followed by a more slow elimination phase (12,20,25). However, one-compartment and noncompartment assumptions have also been used in the calculation of pharmacokinetic values (17,24,26) and even a tri-exponential model has been suggested (27).

One study has been concerned with the distribution of morphine into specified tissue. Following long term infusion the cerebrospinal fluid (CSF):plasma ratio was estimated to be 0.52-1.0 (28). It was suggested that CSF morphine concentration is approximately equivalent to the concentration of unbound morphine in plasma, assuming the protein binding of morphine to be 30%, but no definite relationship between morphine concentrations in plasma and CSF was established. The assumption that protein binding in children is similar to that in adults seems to be an overestimation as mean protein binding has been reported to be 18–22% in preterm and term neonates, and infants up to the age of 2.5 years (13,20) and 20–35% in adults (23). Because protein binding is relatively low in both populations, the difference in protein binding between neonates and infants, and adults will probably make the discrepancy in free morphine plasma concentration too small to be of any clinical relevance, keeping in mind the individual variation in morphine kinetics.

The reported mean values for volume of distribution are shown in Figure 1. There is uniformity between the values irrespective of age of the neonates and children studied; meta-analysis yields a mean value for volume of distribution of $2.8 \pm 2.6\ \mathrm{l \cdot kg^{-1}}$. All reported values have large standard deviations resulting from great individual variation in volume of distribution. The diverging value of $12.9\ \mathrm{l \cdot kg^{-1}}$ found by Dagan *et al*. may be explained by the fact that they studied children following cardiac surgery and therefore children with an altered cardiovascular status, who could have a distribution that differs from the rest of the children studied (29).

Reported values of volume of distribution from studies that were not eligible for meta-analysis, all correspond well to those included in the analysis, i.e. to $2.8 \pm 2.6\ \mathrm{l \cdot kg^{-1}}$.

Half-life

Elimination is almost always described by a single elimination rate, but it has been suggested that the elimination phase is ended by a long terminal half-life of 24.8 ± 4.6 hours (30). This high value is probably not only a result of elimination, but also of redistribution from peripheral tissue into plasma.

Table 2
Gestational and postnatal age of the children included in the studies presented in Figures 1, 2 and 3.

No.	*Reference*	*Gestation*	*Postnatal age*
Preterm neonates			
1	Bhat *et al.* (20)	<30 weeks	<5 days
2	Choonara *et al.* (12)	24–37 weeks	3–12 days
3	Hartley *et al.* (32)	26–34 weeks	<24 h
4	Barrett *et al.* (26)	26–40 weeks	1–5 days*
5	Chay, Duffy, Walker (17)	28–36 weeks	0–3 days
6	Bhat *et al.* (20)	31–27 weeks	<5 days
7	Pokela *et al.* (31)	31–36 weeks	0–2 days
8	Farrington *et al.* (24)	32–36 weeks	1–9 days
Term neonates, infants, and children			
9	Pokela *et al.* (31)	–	0–3 days
10	Chay, Duffy, Walker (17)	–	0–4 days
11	Bhat *et al.* (20)	–	<5 days
12	Lynn, Slattery (22)	–	1–4 days
13	Farrington *et al.* (24)	–	1–6 days
14	McRorie *et al.* (13)	–	1–7 days
15	Koren *et al.* (30)	–	1–9 days†
16	Choonara *et al.* (15)	–	3–15 days
17	McRorie *et al.* (13)	–	8–30 days
18	Pokela *et al.* (31)	–	8–57 days
19	Olkkhola *et al.* (25)	–	11–180 days
20	Lynn, Slattery (22)	–	17–65 days
21	McRorie *et al.* (13)	–	31–90 days
22	McRorie *et al.* (13)	–	91–180 days
23	Dahlström *et al.* (27)	–	0.1–0.8 yrs
24	Pokela *et al.* (31)	–	0.2–0.4 yrs
25	Vandenberghe *et al.* (36)	–	0.2–5 yrs
26	McRorie *et al.* (13)	–	0.5–2.5 yrs
27	Dagan *et al.* (29)	–	0.7–7 yrs
28	Dahlström *et al.* (27)	–	1–7 yrs
29	Olkkhola *et al.* (25)	–	2–4 yrs
30	Olkkhola *et al.* (25)	–	6 yrs
31	Robieux *et al.* (37)	–	prepuberty
32	Robieux *et al.* (37)	–	puberty
33	Dahlström *et al.* (27)	–	7–15 yrs‡
34	Dahlström *et al.* (27)	–	7–15 yrs§
35	Nahata *et al.* (35)	–	11–15 yrs
36	Robieux *et al.* (37)	–	postpuberty
37	Choonara *et al.* (12)	–	1–16 yrs
38	Attia *et al.* (38)	–	4.5–15 yrs
39	Greene *et al.* (28)	–	age not reported

* Two children were 30 and 49 days old; † One child was 37 days old; ‡ Single dose; § Repeated dose regimen
The numbers at the left correlated to the reference number on the x-axis in the figures. Studies describing pharmacokinetic parameters in only one or two children are not included.

Table 3
Estimated values for volume of distribution (Vd), half-life ($t^1/_2$) and clearance (CL) of morphine in preterm and term neonates, infants and children.

	Vd $l \cdot kg^{-1}$	$t^1/_2$ *h*	*CL* $ml \cdot min^{-1} \cdot kg^{-1}$
Preterm neonates		9.0 ± 3.4	2.2 ± 0.7
Term neonates	2.8 ± 2.6	6.5 ± 2.8	8.1 ± 3.2
Infants and children		2.0 ± 1.8	23.6 ± 8.5

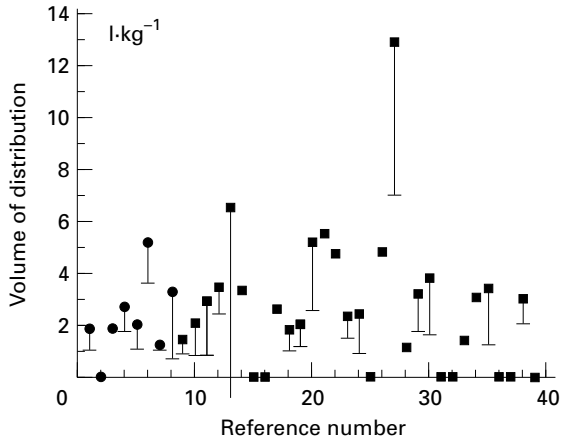

Figure 1
Reported mean values and standard deviations for the volume of distribution of morphine in preterm and term neonates, infants, and children. The reference numbers refer to the studies listed in Table 2, and are ordered according to the age of the children studied.
● Premature neonates; ■ neonates, infants and children.

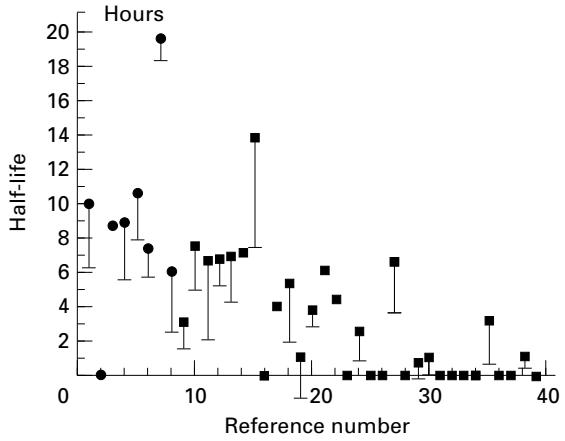

Figure 2
Reported mean values and standard deviations for the half-life of morphine in preterm and term neonates, infants, and children. The reference numbers refer to the studies listed in Table 2, and are ordered according to the age of the children studied.

In Figure 2 are shown reported half-lives of morphine. The tendency that half-life decreases with increasing age can be confirmed by meta-analysis. For preterm neonates the pooled estimate was 9.0 ± 3.4 h, for term neonates aged 0–57 days 6.5 ± 2.8 h, and for infants and children aged 11 days to 15 years 2.0 ± 1.8 h.

Despite differences in study design, indication for morphine usage, analytical procedures and pharmacokinetic assumptions and calculations, results from most of the studies could be included in the pooled estimate for half-life. Three studies reported results that differed significantly; these different results can be explained by dissimilarities in study populations (29,31) and the occurrence of one child with very altered pharmacokinetics (30).

Reported values of morphine half-life from studies that were not eligible for meta-analysis, do all correspond well with those included in the analysis, i.e. to the pooled values for morphine's half-life in preterm neonates, term neonates, and infants and children more than 11 days old.

There are diverging reports concerning the influence of gestational and postnatal age on morphine's half-life. Some claim half-life to be independent of gestational and postnatal age (17,30), while others have correlated half-life to gestational age (26,31) or postnatal age (22).

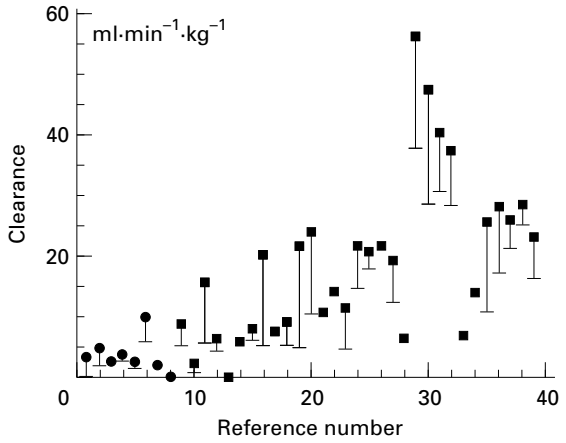

Figure 3
Reported mean values and standard deviations for the clearance of morphine in preterm and term neonates, infants, and children. The reference numbers refer to the studies listed in Table 2, and are ordered according to the age of the children studied.

Clearance

Clearance is the pharmacokinetic parameter that has been studied most intensively (Figure 3).

As expected, clearance increases with age, but it is not possible to derive as consistant a pattern for the development of clearance as for half-life, and reported mean clearance values from less of the children studied can be included in the pooled

estimate. Some of the differences can be explained by disparity in study populations and sampling methods, but the differences might also reflect a very dynamic pattern for the development of clearance rate, which is not easily divided into three groups according to age, as done in the meta-analysis. For preterm neonates the pooled estimate for clearance is 2.2 ± 0.7 ml·min^{-1}·kg^{-1}, for term neonates aged 0–57 days 8.1 ± 3.2 ml·min^{-1}·kg^{-1} and for infants and children older than 11 days 23.6 ± 8.5 ml·min^{-1}·kg^{-1}.

The differences in obtained clearance values for neonates are reflected in different hypotheses concerning the relationship between clearance and gestational age, birth weight or postnatal age. Several studies found no correlation between clearance and gestational or postnatal age (17,30), while other investigators found a significant correlation between clearance and gestational age (20,26,31); Bhat *et al*. even reported morphine clearance to increase with gestational age at a rate of 0.9 ml·kg^{-1}·min^{-1} per week. Also a correlation between clearance and both gestational age and birth weight has been observed (32).

This presentation of the pharmacokinetics of morphine has revealed great intervariability, and to illustrate this with some examples, Chay *et al*. in neonates observed a three-fold variation in morphine half-life and a seven-fold variation in clearance (17). Millar *et al*. registered two-fold variation in morphine steady state concentrations among children receiving morphine infusions with equivalent infusion rates (33). Intrapatient variability has also been reported. Over a ten day period Nahata *et al*. found a two-fold variation in steady state morphine plasma concentration in one patient, who received a constant hourly dose of morphine (34).

Discussion

This review shows that neonates and infants have a metabolism of morphine that is different from adults. It seems that the majority of preterm neonates are capable of conjugating morphine to either M3G, M6G or both, and that birth-weight may be correlated with the glucuronidation capability, but that other factors such as postnatal age also are important. It has been stated that, the glucuronidation capacity of the liver in term neonates and infants is present, but immature at birth, and develops during the neonatal period. It could also be, however, that the deglucuronidation and desulphation processes in neonates and infants are more rapid than the glucuronidation and sulphation reactions, and this is the reason why it is only possible to detect limited amounts of especially M6G and the sulphate glucuronides. One possible metabolic pathway of morphine in neonates and infants that has not been studied is the glucuronidation that might take place in the intestines, and maybe also in the kidneys.

It has been documented that the pharmacokinetics of morphine vary with age, both gestational and postnatal age. Uniform values of volume of distribution are reported yielding a pooled estimate of 2.8 ± 2.6 l·kg^{-1}, and the good correlation to adult values indicates that the distribution of morphine might be considered similar throughout the neonatal period, infancy, childhood and adult life. In contrast to this, half-life decreases and clearance increases with age. Based on the meta-analysis, it appears that preterm neonates have to be regarded as a separate group with regard to half-life and clearance, while the age for distinguishing between term neonates and infants is more uncertain. It has also been revealed that some neonates even from the age of two weeks have a half-life resembling adult half-life, while others do not reach adult value before the age of two months. Regarding clearance, all studies which included neonates younger than one week estimated mean clearance to be below 9 ml·min^{-1}·kg^{-1}, which is lower than adult clearance, and by the age of two months almost all studies, have estimated clearance to more than 20 ml·min^{-1}·kg^{-1}, corresponding to adult clearance. Hence, it seems reasonable to consider, that infants from the age of two months have a half-life and a clearance rate of morphine similar to adults, but it is necessary to keep in mind that in some babies the neonatal period may be as short as two weeks.

The clinical state of the child probably influences the metabolism of morphine and hence the pharmacokinetic parameters. The documentation for this is limited, but clearance has been reported to be reduced during surgery (27), and the cardiac state of the child may influence the elimination rate of morphine (29).

This discussion of the pharmacokinetic parameters of morphine in neonates, infants, and children will be the basis for calculations of recommended dosages for morphine in Part 2.

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