

## Review article

# Drug level monitoring in paediatric practice

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A knowledge of the concentration of a drug in blood or other tissue fluid is now considered an important and sometimes essential part of the therapeutic management of various conditions. Its importance has increased as information showing wide inter-individual variation in drug response has become recognised. Such variation arising from differences in absorption, distribution, and elimination appears to be greater during development, and yet many drugs are still prescribed for children in doses calculated by scaling down adult doses according to weight or surface area.<sup>1</sup>

This conventional dose approach is satisfactory only for drugs with a large therapeutic index (the difference between therapeutic and toxic drug levels is wide). Doses of most drugs need to be individually tailored according to the child's particular requirements. Titration of dose to the therapeutic response is the best means of achieving this. However, this approach is unsuitable for most of the commonly prescribed drugs in children (antimicrobials, anti-convulsants, anti-inflammatory agents, cardiac glycosides) as the response to these is not readily clinically evaluated, and there may be a sub-therapeutic or toxic response. As a result, drugs may be discarded as useless or too toxic.

For many drugs, there is a close relationship between plasma level and therapeutic effect, and the value of knowing the plasma level has been proved for a number of drugs (Table 1). Although fewer data are available for these drugs in children, in the case of most drugs the plasma level—therapeutic response relationship will be better than that between dosage and clinical effectiveness. However, it should be remembered that the clinical effects of some drugs cannot be adequately monitored by

Table 1 Therapeutic ranges for the more commonly used drugs in children

Drug	Therapeutic range ( $\mu\text{mol/l}$ , unless stated)	
	Children	Adults
Phenytoin	20-80 <sup>28</sup> 48-100 <sup>29</sup>	40-80 <sup>30</sup>
Phenobarbitone	40-105 <sup>37</sup>	40-105 <sup>36</sup>
Febrile convulsions	> 60 <sup>39-41</sup> > 63 <sup>42</sup>	
Primidone	Use phenobarbitone	
Carbamazepine		16-50 <sup>47-50</sup>
Sodium valproate	350-700 <sup>57</sup>	240-480 <sup>58</sup>
Diazepam	0.7-1.05 <sup>64-65</sup>	
Ethosuximide	280-700 <sup>67</sup>	
Digoxin	290-500 <sup>68</sup> (adults included)	0.65-2.6 nmol/l <sup>74</sup>
Theophylline		
Asthma	55-110 <sup>81-83</sup>	
Preterm apnoea	30-70 <sup>91-92</sup>	
Salicylate	1000-1800 <sup>94</sup> 2100-2500 <sup>95</sup>	
Gentamicin		
Peak	15 min post IV 60 min post IM	Peak 8.0-18.5 <sup>101-103</sup>
Trough—predose		Trough < 3.7 <sup>104-105</sup>
Tobramycin	11-21 <sup>116</sup>	
Chloramphenicol	30-60 <sup>117</sup>	

concentration measurements, as in the case of cytotoxic agents where there is no temporal relationship between drug level and effect.

### Therapeutic range

Drug concentrations are usually interpreted by the clinician in relation to a known therapeutic range for a particular drug or its metabolite(s), or both. For most drugs, this represents a concentration range associated with optimal therapeutic effect without undue adverse effects in the majority of patients. The ranges suggested for children (Table 1) are in most cases similar to those defined for adults. The usefulness of such a range may be influenced both by the disease process and its severity. Lund<sup>2</sup> showed that the optimal phenytoin level is directly related to

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the severity of epilepsy, and some patients are likely to require concentrations considerably below the accepted range. In addition, if drugs have more than one therapeutic effect, the appropriate range for each must be used. For example, the plasma salicylate range for the treatment of inflammatory conditions, 1000–2500  $\mu\text{mol/l}$ , is considerably greater than that required for general analgesia. Alteration in tissue responsiveness may also affect the levels required for adequate therapeutic effect. In some cases, the usual range may prove too high, as in hypokalaemic patients receiving digoxin, while in others, a greater than usual therapeutic level may be needed in order to overcome the effects of drug tolerance.

### Considerations in interpreting drug levels

**Dose regimen.** The duration of drug therapy, dosage, time since last dose, and dose-frequency must all be known. After starting treatment, a drug will accumulate until the amount eliminated equals the amount absorbed, at which time a steady-state is reached. Unless loading doses are used, this occurs after about five elimination half-lives have elapsed. Drug levels determined during the period of accumulation will underestimate steady-state concentrations.

Once a steady-state has been reached drug concentrations can fluctuate significantly between doses,<sup>3</sup> so the dose-frequency and the time since the last dose must be known. However, for most drugs a 2-fold fluctuation in concentration is generally acceptable, and this occurs when the dose interval approximates the elimination half-life. Even when given at this dose-frequency, the fluctuation is likely to be such that some time is spent with levels outside the therapeutic range during a dose interval. Due to more rapid metabolism, the half-lives of most drugs tend to be shorter in children than in adults, and because of their different social and sleep patterns, frequent drug administration is often impracticable, giving rise to greater fluctuation in plasma levels in the young.

**Active metabolites.** Some drugs form biologically active metabolites (Table 2) and the therapeutic effect of the prescribed drug may rely on the contribution from the metabolite. For drugs like methylphenobarbitone and primidone, the steady-state level of the active metabolite is considerably greater than that of the parent drug.<sup>4</sup> In such cases, measurement of the metabolite instead of the parent compound is reasonable as the therapeutic effect correlates well with the metabolite concentration, although the anticonvulsant effect of the parent drug should not be overlooked. For other drugs, such as carbamazepine, the pharmacological effect of the

Table 2 *Commonly used drugs in children which form active metabolites*

<i>Drug</i>	<i>Metabolite</i>
Allopurinol	Alloxanthine <sup>142</sup>
Amitriptyline	Nortriptyline <sup>143</sup>
Carbamazepine	Carbamazepine 10, 11-epoxide <sup>5-6</sup>
Chloral hydrate	Trichloroethanol <sup>144</sup>
Diazepam	Desmethyldiazepam <sup>145</sup>
Imipramine	Desimipramine <sup>146</sup>
Methylphenobarbitone	Phenobarbitone <sup>147</sup>
Prednisone	Prednisolone <sup>148</sup>
Primidone	Phenobarbitone <sup>149</sup>
Propranolol	4-Hydroxypropranolol <sup>150</sup>

metabolite(s) may be proved in animals,<sup>5-6</sup> but may not have been shown to occur in man. Until further work proves the relevance of such metabolites, their measurement for everyday clinical practice cannot be justified.

**Combination therapy.** The concentration of one drug may be altered by concurrent use of another, and this problem is often seen in paediatric practice as multiple drug prescribing is common.<sup>7-9</sup> In these circumstances, consideration should be given to the possibility that the level may have been increased or decreased as a result of metabolic enzyme inhibition or induction, or that the concentration of the free (active) drug may have been increased by displacement from protein-binding sites. The effects of enzyme induction/inhibition may not be apparent for several weeks,<sup>10</sup> but those relating to changes in protein binding usually occur in the first few days after a drug is added or withdrawn. Protein binding changes are only important for those drugs which are highly protein bound—for example, diazepam,<sup>11</sup> nitrazepam,<sup>12</sup> phenytoin,<sup>13-14</sup> sodium valproate,<sup>15</sup> or in circumstances of abnormal protein binding—for example, uraemia<sup>16-19</sup> and liver disease.<sup>19</sup>

**Patient compliance.** Even when the drug level is known and the above points considered, there remains the possibility that the patient is not complying with instructions. An undetectable level will confirm anxieties about a family's reliability and is easier to interpret than when the concentration is low but detectable. In the latter case, danger may arise when the clinician increases the dose thinking that the low level is due to physiological factors rather than the result of poor compliance.

**Assay reliability.** The reliability of the routine laboratory drug assay service cannot always be assumed<sup>20-21</sup> and interlaboratory quality control schemes, such as that set up for anticonvulsants,<sup>22</sup> should be encouraged.

### Specific drug considerations

Anticonvulsants are frequently prescribed in paediatric practice<sup>8</sup> and often are given in combination. They represent the drug class most commonly implicated in drug interactions in children, further emphasising the need to monitor their levels.

**Phenytoin.** The good relationship between phenytoin levels and anticonvulsant effect is now proved.<sup>2</sup> Its dose-dependent kinetics in children,<sup>23</sup> and adults,<sup>24-26</sup> whereby a small increase in dose results in a disproportionately large rise in plasma level precludes a convenient method for predicting the plasma level from dose except perhaps at low concentrations. The level at which dose-dependent kinetic behaviour begins in children is probably lower than in adults<sup>27</sup> and is likely to occur throughout most of the therapeutic range. Two ranges, 20–80  $\mu\text{mol/l}$ <sup>28</sup> and 48–100  $\mu\text{mol/l}$ ,<sup>29</sup> have been suggested for children, but many clinicians prefer to use the established adult range of 40–80  $\mu\text{mol/l}$ .<sup>2, 30</sup> At the low levels where elimination is first-order, the plasma half-life, a major determinant of concentration fluctuation, is short in children<sup>31-32</sup> and large fluctuations in concentration may occur even when the drug is given at the recommended dose intervals. Two reports suggest that fluctuation is relatively small in children and adolescents taking phenytoin once daily,<sup>33-34</sup> although other workers more recently have found large and unacceptable fluctuations on this regimen.<sup>32</sup>

**Phenobarbitone.** The value of monitoring phenobarbitone levels is considerably less than that of phenytoin. The steady-state levels in children after the neonatal period are reasonably predictable<sup>35</sup> and tolerance to the drug's sedative effect occurs, as it might also do to its anticonvulsant action. A therapeutic range of 40–105  $\mu\text{mol/l}$  has been given for adults,<sup>36</sup> and children.<sup>37</sup> It is difficult to define a level above which toxicity is likely, and some authors have suggested a higher range<sup>38</sup> or given therapeutic levels above 60  $\mu\text{mol/l}$  for children.<sup>39-41</sup> The results of a prospective study suggest that febrile convulsions are controlled when the minimum concentration exceeds 63  $\mu\text{mol/l}$ ,<sup>42</sup> although others have found this to be inadequate.<sup>43</sup> In view of its relatively long half-life in infants and children,<sup>44-45</sup> the degree of concentration fluctuation is likely to be small even when given once daily.

**Primidone.** This drug is converted to two active metabolites, phenobarbitone and phenylethylmalonamide. These are usually present in considerably higher concentrations than the parent drug,<sup>4</sup> and although primidone itself has some anticonvulsant activity,<sup>46</sup> most clinicians believe that

the use of the phenobarbitone therapeutic range gives the best estimate of the drug's clinical effect.

**Carbamazepine.** There is no simple relationship between carbamazepine dosage and plasma concentration. Several therapeutic ranges have been suggested,<sup>47-50</sup> and it seems that levels of 16–50  $\mu\text{mol/l}$  are likely to be optimal. The half-life in children, 4.1–18.3 hours (G W Rylance, D A Priestman, T A Moreland, 1979, unpublished observation),<sup>3, 51</sup> is relatively short, and large fluctuations in concentration occur when the drug is given at recommended dose intervals.<sup>3</sup> Carbamazepine is a potent inducer of both its own<sup>10</sup> and other drugs' metabolism.<sup>52</sup> In children, steady-state levels are less than 20% those expected from single dose pharmacokinetic studies (G W Rylance, D A Priestman, T A Moreland, 1979, unpublished observation). The effect of this induction, which appears to reach a maximum after 2 to 3 weeks of treatment, on the interpretation of carbamazepine levels in the early phase of treatment and on the levels of concurrently used drugs, should be considered carefully. For practical purposes, measurement of the active metabolite, carbamazepine 10,11-epoxide, is not recommended as its activity and levels are considerably less than those of the parent drug.<sup>53-54</sup>

**Sodium valproate.** The usefulness of monitoring sodium valproate levels remains in doubt. Two childhood studies<sup>55-56</sup> were unable to correlate plasma levels with clinical effect, but other investigators have reported a relationship between beneficial and toxic effects and plasma levels both in children and adults, and therapeutic ranges of 350–700  $\mu\text{mol/l}$ <sup>57</sup> and 240–480  $\mu\text{mol/l}$ <sup>58</sup> have been suggested. The poor correlation may relate to the mode of action of the drug<sup>59</sup> or to the pronounced fluctuation in drug level which occurs both within a 24-hour period<sup>60</sup> and from one day to the next.<sup>61</sup> Routine monitoring of sodium valproate in children is not currently recommended, although a recently reported well-controlled study found superior clinical effect at 300–350  $\mu\text{mol/l}$  compared with that at lower levels,<sup>62</sup> suggesting that routine monitoring may soon be justified.

**Diazepam.** There is no established indication for diazepam level monitoring,<sup>63</sup> although two studies in children have suggested that anticonvulsant activity is associated with concentrations of 0.7–1.05  $\mu\text{mol/l}$ .<sup>64-65</sup> The fact that different clinical conditions require different plasma levels, and that brain concentrations of diazepam and its major active metabolite, desmethyldiazepam, vary according to whether treatment is short- or long-term<sup>66</sup> may explain the poor level/effect correlation.

**Ethosuximide.** Prospective studies give good evidence of a plasma therapeutic range for ethosuximide.<sup>67-69</sup> Within the optimal response range of 280–700  $\mu\text{mol/l}$ , drug levels in children can be predicted from the dose given, provided that age is considered.<sup>67</sup>

### Digoxin

The use of steady-state plasma digoxin concentrations as a guide to the drug's clinical effect has been widely canvassed in adult practice,<sup>70-72</sup> although others have questioned this.<sup>73</sup> Infants, who are most likely to require digitalisation, appear to tolerate plasma concentrations above the optimal adult therapeutic range of 0.65–2.6  $\text{nmol/l}$ ,<sup>74</sup> some workers having found concentrations above 4.5  $\text{nmol/l}$  without accompanying toxicity,<sup>75</sup> although others have reported toxicity at these levels.<sup>76-77</sup> As the maximum inotropic effect may be achieved with much lower doses than those usually recommended,<sup>78</sup> concentrations within the adult range may produce a maximum clinical effect in infants. The higher plasma concentrations per unit dose found in very low birthweight compared with 'normal' weight babies<sup>79</sup> may account for the fact that a greater number of ECG abnormalities are seen in preterm babies than in those that are term newborn.<sup>80</sup> The pronounced overlap between toxic and therapeutic concentrations, and the difficulty in assessing clinical effect suggests that routine monitoring of plasma digoxin levels is probably unnecessary in children unless toxicity is suspected. Even then, a raised level itself is not sufficient evidence for intoxication and the level should be interpreted in relation to other factors—such as the dose given, the severity of heart failure, renal function, and the plasma potassium concentration.

### Theophylline

For maximum bronchodilator effect and minimum toxicity, plasma theophylline concentrations should be maintained between 55 and 110  $\mu\text{mol/l}$ .<sup>81-83</sup> The case for monitoring levels is strong as the therapeutic range is clearly established,<sup>81-83</sup> kinetics may be dose-dependent,<sup>84</sup> there is wide interindividual variation in the dose/level ratio,<sup>85</sup> and toxic levels are dangerous.<sup>86</sup> The elimination half-life in children is short<sup>87-89</sup> and there are large fluctuations in concentration if the drug is given at recommended intervals.<sup>85</sup> Fluctuation can be reduced if sustained release preparations are used,<sup>90</sup> but as constant absorption per unit time does not occur, appropriate timing of drug levels and their interpretation depends on the preparation used.<sup>90</sup>

Theophylline is also used for the prevention and treatment of recurrent apnoeic episodes in the

preterm infant. Its efficacy is now established and a therapeutic range of 30–70  $\mu\text{mol/l}$  would seem appropriate.<sup>91-92</sup> The importance of monitoring levels is emphasised by considering the dynamic state of the newborn infant with rapid changes in distribution volumes and maturing enzyme systems affecting drug elimination. Tachycardia as a sign of cardiotoxicity, although sometimes clinically useful, should not be wholly relied on as a guide to theophylline treatment. Multiple sampling in the preterm infant is not without risk, and if possible, a method using small amounts of plasma should be used.<sup>93</sup> Because of the rapid distribution of theophylline in the body, samples drawn midway between doses will reflect the steady-state level fairly closely.

### Salicylate

Although there is no direct relationship between salicylate level and clinical response,<sup>94</sup> two authorities have suggested that levels of 1000–2500  $\mu\text{mol/l}$  should be maintained in children with juvenile rheumatoid arthritis.<sup>94-95</sup> The symptoms of salicylism correlate closely with serum levels and are generally, but not always, present when the level exceeds 2000  $\mu\text{mol/l}$ .<sup>95-96</sup> The case for using drug levels for each treatment is strengthened by the narrow therapeutic index of the drug<sup>94-97</sup> and the large inter- and intraindividual variation in drug level/unit dose, which is perhaps mainly due to the dose-dependent kinetics of the drug,<sup>98</sup> although a report suggests there is a good correlation between salicylate serum levels and dose/ $\text{m}^2$  body surface area.<sup>96</sup>

For general analgesic and antipyretic activity, lower plasma levels appear to suffice.

### Antibacterial drugs

Blood levels of the antibacterial drugs may be presumed to be meaningful measures of drug effect only if bacteraemia is present. Otherwise, the blood concentration is only one of many determinants of drug effect. Other factors, which apply to other drugs too but to antibacterials in particular, are the blood flow to the infected site, the degree of drug protein binding, and penetration of the drug into abscesses, cells, and interstitial fluids.

For optimal effect, drug levels should exceed the mean inhibitory concentration (MIC) for the likely or known causative organism by as great a margin as possible without undue risk of toxicity. However, it should be remembered that the MIC refers to a drug level *in vitro*, and although levels in excess of this are found in the blood, the levels in the infected tissue may be considerably lower. In addition, the controversy about whether high, but poorly sustained

(peak), or lower, but adequate (continuous), levels should be achieved has not been resolved. Although a 'peak' regimen may aid in diffusion of drugs into poorly vascularised areas, and there is evidence that it is effective provided that the interval between doses is not unduly long,<sup>99</sup> it remains unclear which method should be adopted and whether the mode of action of a drug (for example, bacterial wall synthesis inhibition or intracellular protein synthesis inhibition) should determine the type of regimen to be used.

Of the antibacterial drugs, there is a strong case for monitoring levels of gentamicin, tobramycin, and in some circumstances, chloramphenicol.

**Gentamicin.** In adults, peak serum gentamicin concentrations of 7.5–9.0  $\mu\text{mol/l}$  are required for adequate treatment of serious Gram-negative infections.<sup>100–102</sup> There is an increased risk of 8th cranial nerve damage if serum concentrations rise above 18.5  $\mu\text{mol/l}$ ,<sup>103</sup> and of renal damage if nadir levels are greater than 3.7  $\mu\text{mol/l}$ .<sup>104–105</sup> Because of the wide interindividual variation in gentamicin disposition and serum levels on similar dosage,<sup>106–108</sup> monitoring of levels is important, especially in children where such variation is likely to be greatest. Although modification of dosage according to a one-compartment first-order model after an initial dose has been suggested,<sup>109</sup> serial measurements are probably advisable as the drug's kinetics are better represented by a two-compartment<sup>110</sup> or even a multicompartment model.<sup>111</sup> The authors proposing the latter model suggested that treatment should be tailored individually for children, based on peak and trough levels after the fourth or fifth dose, which would still be fairly early in the course of treatment.

**Tobramycin.** Information on desirable drug levels of tobramycin is limited. McAllister and Tait<sup>112</sup> stated that the 'usual' dose given to adults produces serum levels of 11–21  $\mu\text{mol/l}$ , and it has therefore been suggested that organisms with MICs <11  $\mu\text{mol/l}$  should be considered sensitive to tobramycin.<sup>113</sup> According to a commercial report,<sup>114</sup> sustained levels above 26  $\mu\text{mol/l}$  are likely to produce adverse effects and should be avoided. Although the incidence of both nephro- and ototoxicity may be marginally less with tobramycin than with gentamicin,<sup>115</sup> and there is little documentary evidence of a relationship between toxicity and drug level, a therapeutic plasma range of 11–21  $\mu\text{mol/l}$  has been suggested and good results shown when such levels were achieved in the treatment of serious infections.<sup>116</sup> Although a relationship between trough level and toxicity has not been found, rising trough levels give warning of accumulation, and if these are kept below 2  $\mu\text{mol/l}$ ,

the corresponding peak level is usually <21  $\mu\text{mol/l}$ .<sup>116</sup>

**Chloramphenicol.** This is now usually reserved for the treatment of the life-threatening diseases, meningitis and epiglottitis. In these circumstances, adequate treatment is imperative, and monitoring of blood levels has been recommended.<sup>117</sup> The common combination of an enzyme-inducing anticonvulsant drug with chloramphenicol in the treatment of meningitis and the resulting decreased levels of the antibacterial drug,<sup>118–119</sup> further emphasise the need to ensure that adequate levels are maintained. A concentration range of 30–60  $\mu\text{mol/l}$  is accepted<sup>117</sup> and as cerebrospinal fluid (CSF) concentrations are consistently 30–50% of those in plasma,<sup>120</sup> CSF levels of the drug will be adequate for all the more usual organisms causing meningitis.

#### Drug monitoring in other body fluids

**Cerebrospinal fluid.** Drug monitoring in CSF is usually limited to those cases of meningitis in which the expected recovery has not occurred—for example, monitoring of ampicillin, penicillin, and chloramphenicol—or in some cases if intraventricular drug injections are used and preinjection levels determined. The preinjection levels indicate the rate of removal of the drug from the CSF and are often used with gentamicin. Levels in excess of the MICs of the likely organisms are required.

As chloramphenicol levels in CSF are consistently 30–50% of those in plasma,<sup>120</sup> and intrathecal/intraventricular injections are unnecessary, CSF chloramphenicol levels may be assessed indirectly using the more practicable plasma sampling.

**Saliva.** Saliva sampling affords a useful method of drug level monitoring as the saliva concentration of drugs which are unionised at plasma pH is usually proportional to the concentration of the free (unbound) drug in plasma.<sup>121</sup> The dissociation constant and the lipid solubility of drugs are important determinants of the saliva/plasma (S/P) ratio of weak acids and bases<sup>122</sup> and this ratio is much affected by saliva pH.<sup>121</sup> Saliva pH varies with saliva flow rate and small changes in the flow rate profoundly affect the appearance in saliva of acidic drugs with pKa values below 8.5 and basic drugs with pKa values above 5.5.<sup>123</sup> Very weak acids and bases behave as neutral drugs<sup>121</sup> which pass into saliva at concentrations equal to the free drug in plasma water.

For appropriate drugs, saliva monitoring has advantages for paediatricians and children, as it allows fluid to be collected by a noninvasive technique at home, school, or hospital without discomfort or

Table 3 *Drugs in saliva: usefulness of monitoring and therapeutic ranges derived from plasma ranges and saliva/plasma ratios*

Saliva monitoring	Drug	Therapeutic range
Useful	Carbamazepine	5–15 $\mu\text{mol/l}$ <sup>147–50 125</sup>
	Ethosuximide	280–700 $\mu\text{mol/l}$ <sup>167 126</sup>
	Phenytoin	2–10 $\mu\text{mol/l}$ <sup>28–29 127</sup>
Possibly useful	Phenobarbitone	25–42 $\mu\text{mol/l}$ <sup>137 39–40</sup>
	Primidone	As above <sup>4 46</sup>
	Digoxin	Not reliable
	Theophylline (in asthma)	30–65 $\mu\text{mol/l}$ <sup>181–83 151</sup>
Not useful	Diazepam	
	Salicylate	
	Sodium valproate	

risk. As saliva levels indicate the free (active) fraction of drug in the plasma, they will reflect changes in the effective drug concentration arising from disease processes, varying albumin concentrations, and drug interactions.

Most reports refer to the use of mixed saliva, and this can easily be collected from children of all ages, although saliva flow stimulation using citric acid crystals<sup>124</sup> may sometimes be required.

Table 3 shows the relative usefulness of saliva monitoring for the more relevant drugs and lists their respective derived therapeutic ranges. The method is especially useful for carbamazepine, ethosuximide, and phenytoin as there is a good correlation between saliva and plasma levels for each of these drugs,<sup>125–127</sup> and this is independent of concurrent drug use, saliva flow rate, or pH.<sup>128–131</sup>

The usefulness of monitoring other drugs in saliva is less clear. Phenobarbitone is partially ionised at the usual saliva pH, and so the S/P ratio varies with saliva pH. However, if the pH is taken into account, a corrected saliva concentration approximating the unbound fraction may be calculated.<sup>132</sup>

Although there is a good correlation between saliva and plasma primidone concentrations,<sup>127</sup> monitoring of this drug is limited by the problems associated with phenobarbitone monitoring.

The reported plasma digoxin S/P ratios in adults suggest that there is a wide interindividual variation,<sup>133–135</sup> which is not accounted for by differences in digoxin protein binding.<sup>134</sup> Single specimens are probably of little value therefore, although serial sampling in the same individual may be useful.<sup>134</sup> However, Joubert *et al.*<sup>136</sup> suggested that saliva digoxin levels may be better indices of pharmacological effect than plasma levels, as the PTQ index, which relates to electrocardiographic change, correlates more closely with mean saliva than mean plasma digoxin levels. Like digoxin, saliva theophylline monitoring is limited in adults by the large inter- and intraindividual variation in the S/P ratio,<sup>137</sup> and a similar problem may exist in children. In addition, no explanation has yet been

found for the variation of S/P ratio according to time of sampling,<sup>138–139</sup> raised values being found in the first few hours after dosing.

According to the available evidence, saliva is not useful for monitoring diazepam,<sup>140</sup> salicylate,<sup>137</sup> or sodium valproate.<sup>141</sup>

This review has attempted to provide a paediatric perspective of drug level monitoring, outlining the indications, considerations, and pitfalls. Some drugs (for example, lignocaine, mexiletine, procainamide, quinidine, disopyramide, lithium, tricyclic antidepressants) have been omitted from discussion as they are rarely used in paediatric practice. Individual treatment, by monitoring drug levels, would seem to be particularly important for children in view of the pronounced interindividual and age-related variation in drug response throughout childhood. However, it should be stressed that such monitoring is no substitute for sound clinical judgment, and comprehensive examination and assessment of children receiving drugs. It is only when optimum and complementary use of both approaches is realised that children will benefit most.

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