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Guidelines for Rectal Administration of Anticonvulsant Medication in Children

Sarah Smith Research Pharmacist
Centre for Health Studies, University of Durham, 32 Old Elvet, Durham DH1 3HN, UK.
Tel +44 (0) 191 374 1838; Fax (0) 191 374 1843; Email S.C.Smith@durham.ac.uk

Ian Sharkey Principal Clinical Pharmacist
Royal Victoria Infirmary, Queen Victoria Road, Newcastle upon Tyne NE1 4LP, UK

David Campbell Head of Pharmacy
University of North Durham, North Road, Durham DH1 5TW, UK

Abstract

A detailed literature search combined with a comprehensive review of pharmacokinetic data for antiepileptic drugs has been undertaken. A drug was considered suitable for rectal administration if it was absorbed well from the gastro-intestinal tract and it underwent minimal first pass metabolism. Guidelines were compiled with individual drug monographs and practical administration advice for medical and nursing staff.

Pharmacokinetic data and literature evidence support the rectal administration of carbamazepine, clonazepam, diazepam, lorazepam, phenobarbitone and sodium valproate. Phenytoin is poorly soluble and is not absorbed well from the rectum. Gabapentin is absorbed via an active transport mechanism in the gastrointestinal tract so does not possess the ideal pharmacokinetic properties for rectal administration. Vigabatrin and lamotrigine may be suitable for rectal administration although studies are required.

The guidelines compiled include information on dosage, formulation and technique of administration. The rectal route is a useful, yet potentially under-utilised method for delivering anticonvulsant medication when oral administration is not possible. It enables medication to be continued when children with complex neurological problems present for surgery.

Key words: Anticonvulsants – Rectal route – Guidelines

Introduction

Optimal seizure control in epilepsy is dependent on maintaining therapeutic serum concentrations of appropriate anticonvulsants[1]. When continuous oral treatment is not possible due to, for example, illness or surgery, seizure control can become problematic. Patients with severe seizure disorders, such as those patients with cerebral palsy, can present as even more complex cases, as they are frequently taking complex anti-convulsant treatment regimes, which often include newer adjunctive therapies[2]. If adequate blood levels of regular anticonvulsants are to be maintained in such patients, alternative routes of administration need to be considered.

Many of the anticonvulsants do not have parenteral formulations and often intravenous phenobarbitone, phenytoin or a benzodiazepine must be used. There are several reasons why this is undesirable:

- in many cases these drugs may have already been used and failed to control seizures.
- high levels of drugs in the blood after intravenous administration may lead to increased side effects, particularly sedation.
- switching therapies in otherwise well controlled patients is not to be taken lightly as it may add to their clinical complications.
- parenteral administration of drugs to children should be avoided if there is a therapeutically acceptable alternative, to minimise distress to the child.

It is important to recognise the rectal route of administration as an alternative method by which antiepileptic medication can be delivered when oral therapy is impractical or impossible, or when IV administration is not possible or is undesirable. Many drugs can be easily introduced, retained and absorbed from the rectal cavity.

Anti-epileptic Treatment

Established anti-epileptic agents include carbamazepine, phenytoin, phenobarbitone, clonazepam and sodium valproate. Aceta-zolamide, clobazam and primidone are occasionally used and more recently vigabatrin, gabapentin, lamotrigine and topiramate.

Treatment with a single agent is preferred, as multiple drug regimes confer no benefit over monotherapy in 90% of patients while increasing the risk of side effects[3]. Sodium valproate and cabamazepine are often considered as the drugs of first choice in epilepsy as they have few unwanted effects[1].

For some patients seizure control is not possible using one agent alone. The goal of therapy is to provide seizure control with minimum adverse effects and toxicity. Newer anti-epileptic drugs e.g. vigabatrin, lamotrigine, gabapentin and topiramate may be useful as adjunctive therapy for patients with partial or secondary generalised seizures[3].

Rectal Administration of Anti-epileptic Drugs in Children

The rectal route of administration of anticonvulsants is a useful and relatively simple alternative for patients who are unable to take their medication orally. Many anti-epileptic drugs have been administered successfully by this route in the form of suppositories, suspensions or solutions[4-6].

Suppositories, although being more convenient, have relative inflexibility in dosing and may be associated with more erratic and incomplete absorption of medication[5]. Liquid preparations improve flexibility of dosing and allow maximal rectal and colonic mucosal contact, which results in more rapid and complete absorption when compared with suppositories[4,6].

Rectal Absorption

Rectal absorption occurs by passive diffusion across a lipid membrane, in the same manner as in the rest of the gastro-intestinal tract. The extent and rate of absorption are optimal if the drug is lipid soluble and non-ionised[6].

If a drug is absorbed to a significant extent following oral administration then it can be expected to be absorbed rectally[7]. Any major difference would be due to available surface area. In most adults the rectum is 10 to 15 cm in length, 15 to 35 cm in diameter and normally an empty flat organ. The rectal epithelium consists primarily of columnar or cuboidal cells without villi. This results in a surface area of between approximately 200 and 400 cm^2 compared to 2 million cm^2 in the small intestine. This can be rate limiting in drug absorption, as it represents about 1/10,000 of the surface area of the small intestine. The goblet cells secrete mucous with a total volume estimated at approximately 3 ml, spread over a surface area of between 200 and 400 cm^2 at pH = 7.5.

The dosage form is critical to both the rate and extent of absorption after rectal administration. Rectal absorption occurs very rapidly from solutions (e.g. diazepam and valproic acid) whereas suspensions and suppositories tend to produce a slow, continuous absorption[5]. In comparison to the stomach and duodenum, the quantity of fluid available for drug dissolution in the rectum is small, approximately 3 ml in adults, therefore dissolution may easily be the rate-limiting step for poorly soluble substances such as phenytoin[8].

On crossing the mucosal membrane, the drug enters the rich vascular bed of the rectum. Venous return is via the superior, middle and inferior rectal veins. The inferior and middle veins bypass the hepatic portal circulation and drugs administered in the lower portion of the rectum avoid first pass elimination in the liver.

Data is available describing the anatomic dimensions of rectal length, diameter and distended volume capacity in the adult[7]. Data from the Arkansas Children's Hospital has enabled

the age-related changes in rectal length and diameter to be determined, and rectal volumes in normal infants have been calculated. These data can be used to determine the distance at which the enema catheter should be inserted and the volume that can be instilled, and are listed in Table 1[4].

Technique of Administration

As the contents of the rectum can have an effect on the absorption of drug, the rectum should be evacuated prior to drug administration[4]. A cleansing enema should be administered e.g. Fletchers phosphate enema, depending on local policy.

Once prepared, a soft catheter with a single distal hole should be inserted at one half of the rectal length. This ensures that the enema will remain in the distal rectum which permits predictable absorption whilst minimising the risk of perforation.

The appropriate dose of anticonvulsant can be administered by retention enema either in their liquid form or as tablets mixed with water. As mentioned earlier, retention enemas are preferable to suppositories, as the solution used allows maximal rectal and colonic mucosal surface area to be exposed to the anticonvulsant permitting more rapid absorption[4].

Unless diluted, valproic acid and carbamazepine will lead to catharsis. Valproic acid and carbamazepine suspensions should be diluted with equal volumes of tap water. The large volumes, which result, are best administered as microenemas as described later. The appropriate volume can be drawn up into a syringe and administered via a catheter. Those highly soluble drugs e.g. diazepam and lorazepam require only a small volume of solution to be administered so the catheter must be voided of all drug with a small volume of air.

Proctitis is a possible side effect resulting from the administration of these drugs rectally, but in previous studies, this has not been a significant problem[4].

Criteria for Assessment of a Drug's Suitability for Rectal Administration

The main points to consider in assessing the suitability of a drug for rectal administration are as follows:

Absorption from the gastro-intestinal tract

Absorption, throughout the gastro-intestinal tract, is by passive diffusion across a lipid membrane[7]. Whether a drug is administered via the oral or the rectal route, the process by which absorption occurs is the same, therefore a drug which exhibits good absorption when given via the oral route can be expected to be absorbed well from the rectum. Relative surface areas may be rate limiting in drug absorption. Rectal absorption rate is also dependent on the drug's lipid solubility and degree of ionisation in rectal fluids.

Degree of first pass metabolism

After absorption from the gastro-intestinal tract, drugs are transported via the portal circulation to the liver. Many lipid soluble drugs are metabolised extensively when they reach the liver (first pass effect) which results in a marked reduction in the systemic bioavailability of the administered drug. These drugs are typically given in higher doses to compensate for this first pass effect and therefore achieve adequate concentrations in the blood. When a drug is given rectally, a proportion of drug in the lower part of the rectum avoids first pass metabolism. Such drugs, if given rectally at the same dose as required for oral administration, may achieve much higher concentrations in the blood. This increased bioavailability may result in toxicity.

Table 1. Age related changes in rectal dimensions

Age	Diameter (cm)	Length (cm)	Volume (ml)	Length to insert catheter (cm)
1 month	1.5	3	7	1.5
3 months	3.0	6	42	3
1 year	3.5	7	67	3.5
2 years	4.0	8	100	4
6 years	4.5	9	143	4.5
10 years	5.0	12	235	6

A drug, which is not subject to significant first pass metabolism, should not exhibit a marked increase in bioavailability when given at the same dose rectally.

In assessing the suitability of a drug for rectal administration, it is necessary to consider the degree of its first pass metabolism. If it is not significant, the rectal dose is the same as that given orally. In the case of antiepileptic drugs, the rectal route should only be used if first pass metabolism is minimal. Initial doses should not be altered, as it is difficult to predict the level of drug in the blood that will be achieved. Closer monitoring of therapy is essential if the rectal route is used[4].

Carbamazepine

The gastro-intestinal absorption of carbamazepine is slow, erratic and unpredictable but the bioavailability is between 85 and 100%. It undergoes little first pass metabolism[9].

The bioavailability of rectally administered carbamazepine suspension has been compared with the oral tablet and oral suspension[10]. There was no significant difference in total absorption, maximum serum concentration and time to reach maximum serum level between the orally administered tablet and the rectally administered suspension. However, the orally administered suspension was absorbed more quickly and completely. All subjects who were administered the suspension rectally reported a strong urge to defecate. This was thought most likely to be due to the high osmolarity of the suspension. Further dilution of the suspension would decrease this effect but the resulting larger volume would have to be given in small multiple doses. The investigators advised that if defecation occurred within the first 2 hours after a dose then the dose should be repeated. The slow rate of absorption after rectal administration precludes the rectal route in status epilepticus but is useful for maintenance therapy when oral medication cannot be taken.

Similar findings have been reported in another study although absorption was seen to be somewhat slower[11]. Total absorption from the rectal route was comparable to the oral route if the mixture was not defecated within the first 2 hours of administration.

Further studies have shown that when carbamazepine suppositories were administered to volunteers, the bioavailability was 67% of that of the tablets, although rectal absorption was more consistent than the oral route[12].

A commercially available suppository is available. Suppositories of 125 mg can be considered to be equivalent in therapeutic effect to tablets of 100 mg but final adjustment should depend on clinical response[13].

In summary, the rectal administration of carbamazepine suspension gives higher bioavailability than suppositories. Therefore if the suspension is used the same total daily dose should be given but administered in small, dilute multiple doses.

Phenytoin

The absorption of phenytoin following oral administration is limited and slow with a bioavailability of approximately 90%[9]. It does not experience significant first pass metabolism. The literature on the rectal administration of phenytoin is limited. Phenytoin administered rectally is poorly absorbed, and it has been shown that patients maintained successfully on oral phenytoin are unable to maintain therapeutic serum levels of phenytoin if the drug is given rectally[8].

Altering the base used may improve results, and this may be critical for rectal absorption due to the low solubility of phenytoin[6]. This poor absorption can be predicted from its limited absorption in the rest of the gastro-intestinal tract.

Sodium Valproate

Absorption of sodium valproate is both rapid and complete, and it experiences little first pass metabolism[9]. Valproic acid is absorbed when given rectally. Rectal administration is useful in the maintenance of serum drug concentrations and in the treatment of status epilepticus[6]. No commercially available rectal formulations exist, but suppositories are available on a named patient basis. These are only available in the 300 mg strength, which restricts dosing variation, and this can be a particular problem with doses for children.

Absorption following the rectal administration of suppositories in a cocoa butter base containing either sodium valproate 600mg or valproic acid 520mg has been investigated[14]. The absorption of valproic acid from the suppositories was faster than that of sodium valproate, but not significantly different from that of oral sodium valproate.

A study comparing the serum concentrations of sodium valproate tablets against suppositories found that the bioavailability of the suppositories, based on the area under the curve (AUC), is 1.3

times greater than that of tablets therefore the dose of suppositories could theoretically be 75% of that of the tablets[12]. Although differences in bioavailability between tablets given orally and suppositories were observed, it was concluded that replacing tablets with equal doses of suppositories was justifiable. Practical problems of suppository administration included disrupted absorption due to defecation, which may lead to a fall in serum concentration.

The rectal administration of the oral solution has been investigated and showed that oral and rectal administration of valproic acid results in rapid and comparable absorption[15]. Dosage can be varied more accurately by using the oral solution as a retention enema. In a study using commercially available valproic acid solution administered both orally and rectally in children, at a dose of 40mg/kg, the bioavailability of rectal valproic acid was found to be similar to that following oral administration. Although small differences in AUC were observed when changing the route of administration, these were minimal and did not necessitate valproic acid dose adjustments. This study concluded that dosage requirements for rectally administered valproic acid are similar to those for the orally administered drug, and this is a satisfactory alternative when the oral route is unavailable.

Rectally administered valproic acid has been found to be relatively free of adverse effects other than those normally associated with the drug when given by other routes. However, despite 1 to 1 dilution with tap water some children promptly expel the drug, necessitating re-administration.

Phenobarbitone

Absorption of phenobarbitone is slow but complete and first pass metabolism is minimal[9]. There is relatively little information regarding the rectal administration of phenobarbitone.

Phenobarbitone suppositories, prepared extemporaneously using the sodium salt and witepsol, have been administered to patients rectally at doses of 10mg/kg and compared with the same dose administered intravenously, orally and intramuscularly[16]. There were no significant differences in the amounts absorbed via the four routes, however, suppositories were more rapidly absorbed than the intramuscular and oral route.

The suppositories must be prepared extemporaneously, therefore may not be available when needed. The parenteral or oral preparations are more accessible. The elixir contains 15 mg/5 ml phenobarbitone in an alcohol and sucrose base, and due to the low concentration and sucrose base it is not suitable for rectal administration. The parenteral preparation, phenobarbitone sodium containing 30 mg/ml in a primarily propylene glycol vehicle, is more appropriate. Propylene glycol may increase rectal absorption due to its lipid solubility. In addition, phenobarbitone is a weak acid and therefore approximately 50% may be ionised in the neutral pH of the rectum.

The relative bioavailability of rectally administered phenobarbital sodium parenteral solution has been studied. Seven healthy adult male volunteers were given phenobarbitone at a dose of 5 mg/kg intramuscularly and rectally on two separate occasions, five weeks apart. The rectal dose was administered undiluted and retained for at least 4 hours. Subjects remained supine for 30 minutes after the rectal administration. Phenobarbitone sodium was well absorbed rectally with a mean relative bioavailability of 90%, although the absorption was slow so may not be useful in emergencies[17].

In conclusion parenteral phenobarbitone solution is well absorbed rectally and provides a practical useful alternative route of administration.

Diazepam

Diazepam is well absorbed when given rectally. The speed of absorption depends on the formulation used. Commercial preparations that are specifically intended for rectal use are available e.g. Stesolid® (rectal tubes)[13]. Parenteral solutions (not lipid emulsions) can be administered rectally as they are also formulated in a propylene glycol vehicle and absorption is rapid and extensive. Rectal diazepam is usually used for the acute treatment of seizures rather than maintenance[6].

Reported side effects following the rectal administration of diazepam include sedation, drowsiness and light-headedness. Respiratory depression is possible and may occur in up to 8.8% of patients[18].

Clonazepam

The rectal administration of clonazepam suspension in a propylene glycol base has been studied. Peak values following administration occurred with 10–30 minutes compared with that of diazepam (30–60 minutes). Serum values after rectal administration were found to be comparable to the levels found after intravenous administration excluding the first 10 minutes[19].

In other research the commercially available parenteral preparation of clonazepam was diluted and administered rectally. Plasma concentrations indicated that it was rapidly absorbed[20].

Although no pharmacokinetic studies have been published it appears that crushed clonazepam tablets mixed with water and administered rectally may also be effectively absorbed[5].

Therefore, rectal clonazepam appears to be a useful alternative in the treatment of acute seizures and also for maintenance therapy.

Lorazepam

Lorazepam has been recommended as an alternative benzodiazepine in status epilepticus. The parenteral solution has been administered rectally in doses of 50–100 mcg/kg and is well tolerated[21]. Lorazepam would usually be used in the acute treatment of seizures.

Gabapentin

Gabapentin is well absorbed orally with 50–60% bioavailability and no first pass metabolism. The manufacturers of Neurontin® have not completed any specific studies using the rectal route of administration.

Gabapentin is not available in an oral liquid or parenteral formulation but the tablets dissolve in water. The drug is absorbed by an active transport mechanism and is ionised at physiological pH. Gabapentin does not therefore possess the ideal properties for rectal absorption. A study used to determine the extent of absorption of gabapentin after rectal administration to children on maintenance therapy has confirmed this fact[22].

Rectal administration of gabapentin is not a satisfactory alternative when oral administration is interrupted. When gabapentin therapy is temporarily discontinued clinicians should consider administering alternative antiepileptic drugs that can be administered parenterally or rectally.

Lamotrigine

No available literature exists relating to the rectal administration of lamotrigine. It is well absorbed and has a bioavailability of 98%, with negligible first pass metabolism[23]. No information could be obtained from the manufacturer, but as with the other anticonvulsants mentioned it is possible to use the pharmacokinetic data as a predictor of rectal absorption.

It is likely that rectal administration of lamotrigine would be a useful alternative when oral therapy is interrupted although at present there are no pharmacokinetic studies to support this. The dispersible tablets should be used.

Vigabatrin

As with lamotrigine no literature could be found relating to the rectal administration of vigabatrin, however pharmacokinetic data suggests that rectal absorption may be adequate. Oral administration is rapid and complete and vigabatrin undergoes no first pass metabolism[24]. It is suggested that the same dose could be used rectally as is recommended orally. The sachets should be reconstituted with water.

The case study that follows supports the suggestion that both vigabatrin and lamotrigine could be used successfully using the rectal route.

Case study

Relatively little information can be found in the literature regarding the rectal use of newer antiepileptic drugs. We report below the case of a cerebral palsy patient admitted for gastrointestinal surgery who was managed at home with vigabatrin 800 mg orally twice daily and lamotrigine 20 mg orally twice daily. Faced with the problem of maintenance of seizure control, three options existed: to withhold medication, to substitute with an alternative preparation or to use rectal administration using empirical doses based on available pharmacokinetic data. The last option was preferred. The same dose of lamotrigine was administered as a retention enema (20 mg twice daily as a solution of the dispersible tablets and water). Vigabatrin was also given rectally at the same dose (800 mg twice daily using the dispersible sachets).

Although comparative blood levels were not obtained, there was no apparent loss of seizure control. No signs of toxicity were observed and the patient's mother commented that the patient appeared "to become more settled". This may have been because this patient suffered with chronic vomiting, regurgitation and abnormal gastro-oesophageal function (quite typical for cerebral palsy patients), that was bypassed using the rectal route for administration.

Conclusion

Rectal administration of anticonvulsants is a useful alternative when oral administration is not possible. Differences in physical properties and

Table 2. Rectal administration of antiepileptic drugs – summary

Drug	Clinical use of rectal route	Preparation to use for rectal route	Dose	Comments/extra instructions	Supporting data (references)
Carbamazepine	Maintenance	Suppository Suspension	125mg = 100mg oral Same TDD as oral	– Small dilute multiple doses	10,13 11,12
Clonazepam	Acute	Oral solution Injection	0.02–0.1mg/kg 0.05–0.1mg/kg	Undiluted Diluted	18 19
Diazepam	Acute	Rectal tubes	>3years → 10mg 1–3 years → 5mg	Administer according to manufacturer's instructions	10
Gabapentin	None	N/A	N/A	N/A	21
Lamotrigine	Maintenance	Dispersible Tablets	Same TDD as oral	Dissolve in small amount of tap water immediately prior to administration	Based on pharmacokinetic data
Lorazepam	Acute	Injection	0.05mg/kg	Undiluted	20
Phenobarbitone	Maintenance	Injection	Same TDD as oral	Undiluted	16, 17
Phenytoin	None	N/A	N/A	N/A	8
Sodium valproate	Maintenance or acute	Oral liquid	Same TDD as oral	Dilute 1:1 with tap water	6, 11, 12
Vigabatrin	Maintenance	Powder (sachets)	Same TDD as oral	Dissolve in small amount of tap water immediately prior to administration	Based on pharmacokinetic data

TDD = Total daily dose

formulations determine the rate and extent of absorption. Rapidly absorbed drugs e.g. diazepam and lorazepam are suitable for the management of acute seizures whilst drugs that are absorbed more slowly may be more appropriate for maintaining seizure control.

Data exist which support the rectal administration of carbamazepine, sodium valproate, phenobarbitone, diazepam, lorazepam and clonazepam. Studies have demonstrated the lack of efficacy of phenytoin and gabapentin. The physical characteristics and pharmacokinetics of lamotrigine and vigabatrin may make rectal administration pharmacologically practical although there are no studies to support this.

All the data are summarised in Table 2.

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