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# Physician Preference for Antiepileptic Drug Concentration Testing

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**A four-item questionnaire asked active U.S. members of the Child Neurology Society to value painless antiepileptic drug concentration monitoring, whether members had ordered a saliva level (the best established painless method) in the last year, and whether such levels were available. Value was quantified by time per patient that the physician would willingly expend to arrange for the test. Of 945 questionnaires sent, 544 (58%) were returned. When asked the value of a painless method for children, 286/522 (55%) reported willingness to expend 10 to 30 minutes to arrange the test; 498/522 (95%) would use a painless method if available. When asked the value of an immediate sample at home during a seizure or adverse event, a substantial majority, 370/526 (70%), would make an important donation of their own time to arrange for the sample. Only 5% would not use it. Just 2/544 respondents had obtained a painless (saliva) concentration, and merely 33/544 (6%) perceived such tests as being available. We conclude that child neurologists put a high value on painless antiepileptic monitoring. These data suggest that a painless method of measuring antiepileptic drug concentrations—especially if it could be performed at home—would fulfill an unmet need in the care of children with epilepsy.**


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## Introduction

Successful treatment of epilepsy often requires the monitoring of antiepileptic drug concentrations. Within the usual therapeutic ranges for these drugs, most children have good seizure control with minimum adverse effects [1]. Monitoring antiepileptic concentrations is also useful in evaluating patient adherence to the treatment plan [2] and for monitoring the variations induced by changes in weight and metabolism as children grow [3]. The review articles that guide American physicians mention using other tissues to monitor antiepileptic drug concentrations, but virtually all guidance and usual therapeutic values are given for blood and thus require a venipuncture [2,4,5]. This bias exists in part because of good evidence correlating the effects of the commonly used antiepileptic drugs with serum concentrations. Interestingly, there is also good evidence correlating the effects of the commonly used antiepileptic drugs, phenobarbital, phenytoin, and carbamazepine with concentrations as measured in saliva. Saliva is the alternative body fluid, available without causing the patient pain, that is best suited for therapeutic drug monitoring [6]. Nevertheless, neither review articles nor discussions with colleagues suggest that saliva levels are commonly used in the United States [2,3].

Monitoring with serum antiepileptic concentrations involves some obvious disadvantages. There is the discomfort and fear associated with the venipuncture necessary to obtain serum. Additionally there is the cost and inconvenience of going to a clinic or hospital to have the blood drawn. The problem of discomfort is magnified with children whose age or limited intellectual ability makes it impossible for them to understand why this pain is "for their own good". Moreover, parents may not want to subject a child to this discomfort and thus neglect having their child tested and then miss subsequent clinic appointments [7].

None of these disadvantages occur with saliva monitoring. There is no pain, and no special skill is required to obtain the sample [8].

We have been puzzled by the apparent lack of use of a painless method of therapeutic monitoring. One hypothesis is that the adoption of new technology is dependent

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**Table 1. Responses to questions 3 and 4 about perceived value of test**

| Responses | Question #3 Painless Method for Routine Care | Question #4 Immediate Sample at Home at Time of Seizure or Adverse Event |
|---|---|---|
| Very valuable, I would be willing to spend ½ hour of my time per patient to arrange such a test. | 56 (11%) | 96 (18%) |
| Moderately valuable, I would be willing to spend 10 minutes of my time per patient to arrange such a test. | 230 (44%) | 274 (52%) |
| Not very valuable, I might use such a test but would not spend extra time per patient (to make advance arrangements)* | 212 (41%) | 131 (25%) |
| Of no special value, I doubt that I would use such a test | 24 (5%) | 25 (5%) |
| Totals | 522 | 526 |

* Phrase in parenthesis only used in question 4.

upon physician attitudes and behavior. Thus if saliva monitoring is not being used, this hypothesis posits that physicians are uninterested in the advantages presented by saliva testing, such as reducing discomfort, and further posits that physicians, by not requesting saliva levels, are preventing the adoption of this technology. We investigated these issues by questionnaire, surveying American child neurologists.

## Methods

With permission of the Medical Institutional Review Board, we mailed a questionnaire to each active United States member of the Child Neurology Society. To be an active member, a physician needs to be "certified in Neurology with Special Qualification in Child Neurology by the American Board of Psychiatry and Neurology" or "eligible to take the examination for certification" [9]. The vast majority of these physicians are also eligible for certification by the American Board of Pediatrics.

We had Medical Institutional Review Board permission to identify respondents and to send two follow-up questionnaires to physicians who did not respond initially. The questionnaire consisted of four questions. To encourage responses and to limit the burden on the surveyed physicians, the questionnaire was limited to a single page. The first two questions asked whether respondents had ordered one or more saliva levels in the last year and whether the respondents believed that such levels were available to them. Two additional questions inquired about the perceived value of painless monitoring to their patients in routine practice and at home monitoring in crisis situations. For these last two questions, respondents could choose between the four responses listed in Table 1.

Excluded from the survey were the investigators and their colleagues and research associates.

In advance of the survey, we telephoned 10 national testing laboratories and inquired whether they would perform salivary antiepileptic drug levels. Five laboratories replied affirmatively.

## Results

Of 1006 mailed surveys, 57 were returned by the postal service as undeliverable and four went to members of our research group, giving a denominator of 945 patients. After three mailings, 544/945 questionnaires had been returned (58%). We compared responders and nonresponders, dividing them into the four regions defined by the U.S. Census Bureau [10]. We could find no statistically significant geographic differences between responders and nonresponders. Only 2/544 (0.4%) respondents indicated having obtained a saliva level in the last year (question #1), and just 33/544 (6%) indicated that saliva levels were available to them (question #2). 187/544 (34%) replied that no such levels were available to their practice, and 312/544 (57%) "didn't know" (question #2). Of the 33 positive respondents, 12 were located in the Midwest, 8 in the South, 7 in the East, and 6 in the West with no predominance in any specific cities.

Question #3 asked: "How valuable to the care of your pediatric patients would be the ability to obtain anticonvulsant drug levels by a painless method as opposed to serum which requires a venipuncture?" There were 522 usable responses (Table 1); 286/522 or 55% of responding physicians thought such an innovation valuable enough that they would expend 10 to 30 minutes of their own time to arrange the test, and 498/522 or 95% stated that they would use a painless method if it were available. Question #4 asked: "How valuable to the care of selected patients would be the ability to obtain an immediate sample at home for anticonvulsant level determination at the time of a seizure or adverse event—without the delay necessitated by a trip to a laboratory or emergency department?" A substantial majority of the sample, 370/526, 70% of the physicians, would make a significant donation of their own time to arrange for such a test. Only 5% believed it was not of value (Table 1).

## Discussion

Our survey indicates that child neurologists place a high value on a painless method of monitoring antiepileptic drug concentrations (Table 1). We sought a value judgment from the respondents and avoided the traditional responses "strongly agree", "agree", "neither agree nor disagree", and "strongly disagree". The reason we avoided those responses is that the questions involved pain vs no pain. We were concerned that respondents would believe that for social reasons they were obligated to "agree" with any method that reduced pain whatever their true feelings. Money is commonly used in such surveys to measure value—respondents are asked how much they would be willing to pay to achieve a given outcome. In our opinion, because doctors do not personally finance the care of their patients, this measure would be unrealistic for a physician survey. On the other hand, it is common for physicians to expend their time without additional remuneration in the

care of patients. So we asked physicians to what extent they would be willing to spend their time "to obtain anticonvulsant levels by a painless method" (Table 1). To our surprise 11% of physicians chose the most expensive option, one half hour of their time. Another 44% offered 10 minutes of time, the second option. These two groups outnumbered the 212 physicians (41%) who would use the test but did not believe it warranted an additional time investment.

A number of physicians who chose the third answer, ". . . I might use the test but would not spend extra time per patient", wrote notes on the margin asking if we didn't understand how busy physicians were, didn't we know that there was no extra time in the day to do things such as arrange for tests. They indicated that they actually would value the test highly but could not see how they could invest one half hour or even 10 additional minutes. These responses have encouraged us to believe that the surveyed doctors took the questionnaire seriously and that respondents who volunteered to expend their own time placed a high value in avoiding subjecting children to painful tests.

We also asked respondents how valuable the ability "to obtain an immediate sample at home . . . at the time of a seizure or adverse event" would be. The positive response was overwhelming. Seventy percent would invest 10 to 30 minutes per patient of their own time "to make advance arrangements for such a test".

We have no clear explanation why 70% of physicians were willing to expend their own time (question #4) vs 55% for the preceding question. Perhaps the phrase "adverse event" in this last question triggered a stronger response than the routine situation described in question #4. The differing responses between the questions lends credibility to our impression that the child neurologists who responded read each questions carefully and attempted to give an answer that reflected their best clinical judgment.

The ability to obtain an immediate sample in the home is a potential advantage of saliva monitoring [8,11]. This use has not been widely explored, but the simplicity of sample collection and the stability of specimens at room temperature suggests it could be practical [12]. Especially with epilepsy where seizures can occur infrequently and remembering to adhere to medication schedules can be difficult [2], this option could be especially valuable [13]. In the event that a child has a seizure or possible adverse effect, physicians often need an antiepileptic drug concentration before suggesting a medication adjustment. With serum this entails a visit to a laboratory, or during nights and weekends it means either an emergency department visit or waiting until the laboratory resumes operation. The emergency department visit may not be clinically necessary and incurs further expense. Delaying collection of the sample allows the serum concentration to change so that the measured serum concentration will no longer represent the concentration that existed when the event occurred [14].

Our data suggest that saliva antiepileptic monitoring has not been widely adopted. Among U.S. child neurologists, the patients of this survey, only two respondents had ordered a saliva antiepileptic level in the last year as part of their routine office practice and less than 7% (37/544) reported even knowing of a laboratory which could perform the test. The child neurologists are the pediatric subspecialists with the greatest experience in managing epilepsy. Children with epilepsy constitute a large percentage of their patients. If they do not use an epilepsy-related test and don't even know where to obtain it, in our opinion, it is doubtful if any other group of U.S. physicians caring for children with epilepsy uses it.

Our survey suggests that a painless method of measuring antiepileptic drug concentrations, especially if the technique would lend itself to obtaining samples at home or school, would fill an important and unmet need in the management of children with epilepsy. Using saliva in place of serum might fill that need. Data supporting saliva measurements for phenobarbital, phenytoin, and carbamazepine have been available for over 10 years [15,16]. Recent studies have demonstrated close correlations between serum and saliva concentrations for lamotrigine [17], levetiracetam [18], and topiramate [19]. It is possible that some clinicians also routinely monitor hepatic, hematopoietic, and other factors that require blood samples. Given the lack of value of such monitoring with the above antiepileptic drugs, it is difficult to see that this will be a major issue [2,20,21].

The technique for obtaining saliva is easy enough; the child simply spits into a plastic cup [22]. For infants or children who are unable to cooperate, a simple, disposable pipette can be used to obtain saliva. A drop of citric acid will stimulate saliva production if the child's mouth is dry without altering the assay [22]. The major technological problem is obtaining saliva too close in time to oral administration of medication—traces of medication may remain in the mouth and contaminate the sample. A 3-hour interval is sufficient to avoid this problem [23].

Our survey data strongly suggest that there is an unmet need for obtaining antiepileptic drug concentrations without causing pain, especially if this method could be used at home or school. It is clear that the current leading technology which could meet this need, saliva concentration determinations, has not been adopted. This circumstance does not appear to reflect a lack of physician interest. We do not have data regarding other factors that might inhibit the adoption of this technology. It is possible that economic factors which are beyond physician control, such as the loss of revenue from phlebotomy or the cost to the laboratory of switching from one test to another, have favored the status quo. The lack of proprietary methods that would be promoted by patent holders could also be a factor [14].

Assuming there were no commercial barriers, a pathway for expanding the use of salivary antiepileptic drug concentrations would include demonstrating: (1) The exis-

tence of high and replicable correlations between salivary levels, serum levels, and dose. (2) The ability of families to secure salivary samples at home. (3) That when stored at room temperature and sent by mail to the laboratory, salivary antiepileptic drug concentrations are stable. (4) Children become seizure-free more rapidly when salivary concentrations are obtained immediately after a seizure occurs. (5) Children experience fewer days of drug side effects when salivary concentrations are obtained at the time of any possible adverse event. Also advantageous would be demonstrations that eliminating the need to take their child to the laboratory saves families important amounts of time and money, that avoiding phlebotomy lowers the cost per test, and that families and children prefer saliva collection to phlebotomy.

This questionnaire was limited to a single page. Although this is likely to have improved our response rate, it certainly limited the number and complexity of the questions that could be asked. In addition, the questions asked respondents to report on their current or future behavior. We have no way of determining whether those who predict they would use a test in the future would actually behave in accordance with their responses. We are encouraged by the distribution of responses that we have avoided simply triggering a socially correct response [24].

## Conclusion

When queried, many U.S. child neurologists are willing to expend their own time to arrange for painless antiepileptic drug concentration monitoring for their pediatric patients. An even higher value is placed on obtaining antiepileptic drug concentrations without travel to a medical facility if the child should have a seizure or a potentially adverse event. These responses suggest that the circumstances are appropriate to move away from serum-based antiepileptic drug concentration monitoring and for the widespread adoption of saliva or some similar method for monitoring antiepileptic concentrations for children. This possibility becomes more practical with the increasing numbers of antiepileptic medications that do not require serum surveillance of hematopoietic, liver, or renal function.

### References


**[1]** **Hauser** WA, Hesdorffer DC. Remission, intractability, morality, and comorbidity of seizures. In: Wyllie E, ed. The treatment of epilepsy: Principles and practice. Philadelphia: Lippincott Williams & Wilkins, 2001:139-45.

**[2]** **Leppik** IE. Laboratory tests. In: Engel J, Jr, Pedley TA, eds. Epilepsy: A comprehensive textbook. Philadelphia, New York: Lippincott-Raven, 1998:811-7.

**[3]** **Birnbaum** AK, Kriel RL, Cloyd JC. Pharmacokinetics in infancy, childhood, and adolescence. In: Wyllie E, ed. The treatment of epilepsy: Principles and practice. Philadelphia: Lippincott Williams & Wilkins, 2001:741-57.

**[4]** **Kriel** RL, Birnbaum AK, Cloyd JC. Antiepileptic drug therapy in children. In: Swaiman KF, Ashwal S, eds. Pediatric neurology: Principles and practice. St. Louis: Mosby, 1999:692-718.

**[5]** **Menkes** JH, Sankar R. Paroxysmal disorders. In: Menkes JH, Sarnat HB, eds. Child neurology. Philadelphia: Lippincott Williams & Wilkins, 2002:919-1026.

**[6]** **Pichini** S, Altieri I, Zuccaro P, Pacifici R. Drug monitoring in nonconventional biological fluids and matrices. Clin Pharmacokinet 1996;30:211-28.

**[7]** **Rylance** GW, Moreland TA. Saliva carbamazepine and phenytoin level monitoring. Arch Dis Child 1981;56:637-40.

**[8]** **Bailey** B, Klein J, Koren G. Noninvasive methods for drug measurement in pediatrics. Pediatr Clin North Am 1997;44:15-26.

**[9]** **Child Neurology Society.** Child Neurology Society Directory 2000. St. Paul, Minnesota: Child Neurology Society, 2000.

**[10]** **U. S. Census Bureau.** Census regions and divisions of the United States. http://www.census.gov/geo/www/us_regdiv.pdf. 2002.

**[11]** **Tal** A, Aviram M, Gorodischer R. Variations in theophylline concentrations detected by 24-hour saliva concentration profiles in ambulatory children with asthma. J Allergy Clin Immunol 1990;86:238-43.

**[12]** **Rosenthal** E, Hoffer E, Ben Aryeh H, Badarni S, Benderly A, Hemli Y. Use of saliva in home monitoring of carbamazepine levels. Epilepsia 1995;36:72-4.

**[13]** **Stanaway** L, Lambie DG, Johnson RH. Non-compliance with anticonvulsant therapy as a cause of seizures. N Z Med J 1985;98:150-2.

**[14]** **Berndt** ER. The U.S. pharmaceutical industry: Why major growth in times of cost containment? Health Aff (Millwood) 2001;20:100-14.

**[15]** **Miles** MV, Tennison MB, Greenwood RS, et al. Evaluation of the Ames Seralyzer for the determination of carbamazepine, phenobarbital, and phenytoin concentrations in saliva. Ther Drug Monit 1990;12:501-10.

**[16]** **Miles** MV, Tennison MB, Greenwood RS. Intraindividual variability of carbamazepine, phenobarbital, and phenytoin concentrations in saliva. Ther Drug Monit 1991;13:166-71.

**[17]** **Trnavska** Z, Krejcova H, Tkaczykovam, Salcmanova Z, Elis J. Pharmacokinetics of lamotrigine (Lamictal) in plasma and saliva. Eur J Drug Metab Pharmacokinet 1991;3(Spec No 3):211-5.

**[18]** **Grim** SA, Ryan M, Miles MV, et al. Correlation of levetiracetam concentrations between serum and saliva. Ther Drug Monit 2003;25:61-6.

**[19]** **Miles** MV, Tang P, Glauser TA, et al. Topiramate concentrations in saliva: An alternative to serum monitoring. Pediatr Neurol 2003;29:143–7.

**[20]** **Leppik** IE, Jacobs MP, Loewenson RB. Detection of adverse events by routine laboratory testing [letter]. Epilepsia 1990;31:640.

**[21]** **Wyllie** E, Wyllie R. Routine laboratory monitoring for serious adverse effects of antiepileptic medications: The controversy. Epilepsia 1991;32(Suppl. 5):S74-9.

**[22]** **Gorodischer** R, Burtin P, Verjee Z, Hwang P, Koren G. Is saliva suitable for therapeutic monitoring of anticonvulsants in children: An evaluation in the routine clinical setting. Ther Drug Monit 1997;19:637-42.

**[23]** **Dickinson** RG, Hooper WD, King AR, Eadie MJ. Fallacious results from measuring salivary carbamazepine concentrations. Ther Drug Monit 1985;7:41-5.

**[24]** **Baumann** RJ, Wilson JF, Wiese HJ. Kentuckians' attitudes toward children with epilepsy. Epilepsia 1995;36:1003-8.