Serum sodium valproate testing: is it appropriate?

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ABSTRACT

Objective: To assess whether serum sodium valproate (SVP) testing in the hospital setting is being performed according to evidence-based criteria.

Design and setting: Retrospective audit of serum SVP concentration measurements performed on inpatients and emergency department patients at The Canberra Hospital from May to July 2005.

Main outcome measures: Indication for performing the test, assessed against evidence-based criteria; timing of blood sample collection; whether the test result altered patient management; whether the request form allowed laboratory staff to assess the appropriateness of the test; cost of performing inappropriate tests.

Results: We retrieved 211 test results performed on a total of 95 patients. Notes on 89 patients were available for analysis. Based on evidence-based criteria, 15% of tests were done for an appropriate indication and 29% of the samples were taken at an appropriate time. At most (using generous criteria), 57% of test results made a difference to patient management. Forty-four per cent of request forms contained sufficient detail to allow the pathology department to assess the appropriateness of the test. An estimated $13 236 would be spent unnecessarily on SVP testing at our hospital over a 1-year period.

Conclusions: Most serum SVP level measurements were requested inappropriately, and many were not taken at the correct time, thereby rendering the results uninterpretable. Better education of requesting clinicians could significantly reduce the number of unnecessary tests and thus reduce the cost to the health service.

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Sodium valproate (SVP) is widely used for treating epilepsy, pain syndromes and psychiatric disturbance. Following its introduction in 1960,[1] many studies found that there was a poor correlation between serum SVP concentration and dose. As a result, measurement of serum SVP concentration has been in routine clinical use for over 25 years, with a suggested therapeutic range of 300–700 μmol/L.[2]

Measurement of a trough level is required, so the blood sample has to be taken at least 8 hours after the most recent dose. This requirement is often not met in busy clinical settings and, even when it is, studies have still found a poor correlation between SVP dose and serum concentration.[3-7]

Several studies have further suggested that serum SVP concentration bears little relation to clinical effectiveness (eg, seizure control) or to the magnitude of side effects.[8,9] In fact, a patient's dose of SVP can be adjusted on the basis of clinical parameters (ie, effectiveness in controlling symptoms set against magnitude of side effects). Thus, for day-to-day use, measuring serum SVP concentration is unnecessary.[2,4,10-13] Current evidence suggests that measuring SVP is not clinically useful except in certain situations such as the assessment of toxicity or compliance[7,14,15] or, possibly, in the alteration of dosage for individual patients on polypharmacy.[2] In spite of this, the practice of routine measurement of serum SVP concentration is widespread, particularly in emergency departments (EDs), outpatient departments and general practice settings, and many clinicians are unaware of the significance of measuring trough levels. Audits elsewhere[16-20] have repeatedly indicated inappropriate use of the test.

The cost of SVP testing is considerable. In 2003, 969 SVP tests were performed at The Canberra Hospital (TCH), costing the health service a total of $19 816.05. (The Medicare Benefits Schedule reimbursement amount was $20.45 in 2003 and $18.45 at the time of our study.) Clearly, if tests are being requested inappropriately, there are significant potential savings to be made by tightening the criteria for ordering tests.

We undertook a retrospective audit of requests for serum SVP concentration estimation on inpatients and ED patients at TCH. Our main aim was to assess the magnitude of inappropriate serum SVP concentration testing.

METHODS

Using the ACT Pathology database, we retrospectively examined all requests for serum SVP concentration measurement for inpatients and ED patients over the 3-month period May–July 2005. If multiple tests were performed on an individual patient, the initial test in the list was retained but the remainder were discarded after counting the total number of repeats. All non-duplicated tests were then entered into a database for further analysis. Information about why and when each test was performed was extracted from case notes. All data collected were de-identified. Our study was approved by the TCH Deputy General Manager and the Medical Records Committee.

Patient demographics

For each patient, we noted age, sex, indication for SVP testing, total daily dose, and reason for the current hospital admission. The source of the request (ie, hospital ward or ED) was determined wherever possible.

Indication for performing SVP test (appropriateness)

Indications relating to assessment of compliance, toxicity or overdose were considered "appropriate". All other reasons were deemed "inappropriate", including testing for the purpose of dose adjustment. Repeated tests (ie, tests performed on consecutive days on the same patient) were also considered inappropriate, as were tests for which no reason for performing the test could be obtained from the notes or the request form.

Timing of test (validity)

A test was considered "valid" if the serum sample was taken at trough level (ie, at least 8 hours after the last dose) or if the patient was admitted to the ED with a possible overdose of SVP.

Effect on patient management (impact)

Given the variable standard of note-keeping, a very generous estimate of "impact" was proposed, which was simply whether or not the test result was documented in the patient notes or whether there was an obvi-

1 Patient demographics

	Number (%)
Sex	
Male	47 (53%)
Female	42 (47%)
*Indication for SVP use**	
Epilepsy	59 (66%)
Psychiatric disturbance	27 (30%
Migraine	1 (1%)
Pain	4 (5%)
Other	1 (1%)
Reason for hospital admission	
Epilepsy	29 (33%)
Psychiatric disturbance	14 (16%)
Migraine	1 (1%)
Pain	1 (1%)
Other	44 (49%)
Source of request	
Emergency department	44 (49%)
Hospital ward	25 (28%)
Unable to assess	20 (22%)
Total sets of notes analysed	*89 (100%)*

SVP = sodium valproate. * Three patients had more than one indication. ◆

ous change in SVP dose after the test. Even allowing for inadequacy of medical records, this criterion was thought likely to overestimate the true impact of the test.

Clarity of request form

For each patient, we determined whether there was a legible, clearly stated indication for the test on the request form that would have allowed laboratory staff to assess the appropriateness of the test.

RESULTS

A total of 211 index tests were retrieved. Of these, 116 (55%) were duplicate tests and were therefore not investigated further. For the remaining 95 tests, 89 sets of notes (94%) could be retrieved and analysed.

Patient demographics (Box 1)

The distribution of testing between sexes was about equal, and all age ranges were represented. Most patients were taking SVP for epilepsy (66%) or psychiatric disturbance (30%). The primary reason for hospital admission was related to the underlying condition in about half the cases, and about half of the tests were performed in the ED. The median daily dose of SVP was 1000 mg (range, 200–3000 mg).

Indication for performing SVP test (Box 2)

Five of the 89 tests were performed to assess compliance and eight to assess overdose or toxicity. Thus, a total of 13 tests (15%) were performed for the predefined appropriate indications. If the 116 unnecessary duplicate tests are also taken into account, the number of appropriate tests was 13 out of a total of 205 (6%).

Timing of test

Twenty-six of 89 samples (29%) were valid. The results of all samples are plotted against dose in Box 3. The poor correlation between dose and serum level was unaffected by whether or not the test was performed at the correct time.

Effect on patient management

Five of the 89 sets of notes could not be satisfactorily assessed in terms of the effect of SVP testing on patient management. Among the remaining 84, 48 results were clearly documented in the patient notes, with 18 management changes noted. However, 36 tests (43% of tests recorded in the 84 sets of notes analysed) apparently made no difference to patient management. Hence, at most, 57% of the tests reviewed had an effect on clinical management (Box 2).

Clarity of request form

Thirty-nine of the 89 request forms (44%) were written clearly enough to allow the pathology department to make an informed decision about the appropriateness of the test (Box 2).

DISCUSSION

Our study demonstrated that only 6%–15% of requests for serum SVP level estimation were appropriate when assessed against evidence-based guidelines, and only 29% of samples met the stated criteria for validity. Using the simple criterion of documentation of the result in the patient's notes, 57% of tests had an effect on patient management, but most of these tests would have been either inappropriate or invalid.

The high proportion of inappropriate requests almost certainly reflects a lack of awareness among clinicians of the evidence-based indications for requesting serum SVP level testing. Our results also suggest that many clinicians are unaware of the need for precise timing of the blood sample to obtain a valid measurement. Such errors are a source of substantial unnecessary cost to the health care system.

At a rate of $18.45 per test, the cost of performing all 211 tests requested over the 3-month period was $3893, translating to an estimated annual cost of $15 572. If only 15% of those tests were appropriate, the unnecessary expenditure for this test on the population sampled at TCH amounts to about $13 236 a year.

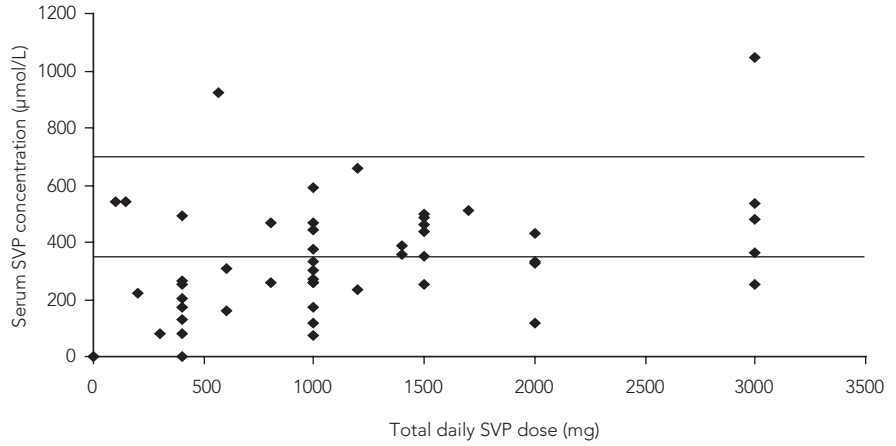
There is no reason to suggest that the practices followed in Canberra differ significantly from those in any other part of Australia. Extrapolating to all tests performed in Australia, a potential saving to the health service of many tens of thousands of dollars

2 Results of analysis of patient notes and request forms

	Number (%)
Indication for performing SVP test	
Assessment of compliance	5 (6%)
Assessment of overdose	3 (3%)
Adjustment of dose	6 (7%)
Assessment of toxicity	5 (6%)
Repeat test	1 (1%)
"? Subtherapeutic"	41 (46%)
"Preoperative check"	1 (1%)
Requested by patient	1 (1%)
No reason given	26 (29%)
Total	*89 (100%)*
Timing of test	
Appropriate (> 8 hours since last dose)	26 (29%)
Inappropriate (< 8 hours since last dose)	32 (36%)
Unable to assess	31 (35%)
Total	*89 (100%)*
Effect on patient management	
Result documented in notes	48 (57%)
Clear change in management as a result of SVP testing	18 (21%)
Result not documented in notes	36 (43%)
Total	*84 (100%)*
Clarity of request form	
Legible/indication clear	39 (44%)
Illegible/indication unclear	50 (56%)
Total	*89 (100%)*

SVP = sodium valproate. ◆

3 Serum sodium valproate (SVP) concentration as a function of daily dose in 89 separate patients*



*The "therapeutic range" for SVP measurements at The Canberra Hospital (350–700 μmol/L) is represented by horizontal lines on the graph.

would result if inappropriate SVP tests could be avoided.

One way to overcome the inappropriate or invalid use of the SVP test would be to have laboratory staff "police" the test and only perform it if the request form indicated that the reason for the test was appropriate and that the sample had been collected in a valid manner. In this context, it is noteworthy that only 44% of forms analysed in our study would have permitted this.

In conclusion, our study shows that most requests for serum SVP concentration measurement are inappropriate when judged against evidence-based criteria. Our suspicion is that similar results would be found if laboratory tests for serum concentrations of many other drugs were examined. Better education of the clinicians who request these tests as to how to manage patients without the need for such measurements, and what the evidence-based appropriate indications actually are, would undoubtedly result in major savings to the health service. Such an education program is currently being set up at TCH, and the effects of this program will be audited in due course.

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COMPETING INTERESTS

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REFERENCES

1 Shorvon S. Handbook of epilepsy treatment. 2nd ed. Oxford: Blackwell, 2005.
2 Arroyo S. Valproate. In: Shorvon S, Perucca E, Fish DR, Dodson E, editors. The treatment of epilepsy. 2nd ed. Oxford: Blackwell, 2004.
3 Lenn NJ, Robertson M. Clinical utility of unbound antiepileptic drug blood levels in the management of epilepsy. *Neurology* 1992; 42: 988-990.
4 Anthony M, Hinterberger H, Lance JW. Plasma sodium valproate levels and clinical response in epilepsy. *Clin Exp Neurol* 1977; 14: 208-215.
5 Vajda FJ, Mihaly GW, Miles JL, et al. Sodium valproate: dose–plasma level relationships and interdose fluctuations. *Clin Exp Neurol* 1978; 15: 145-153.
6 Rowan AJ, Binnie CD, de Beer-Pawlikowski NK, et al. Sodium valproate: serial monitoring of EEG and serum levels. *Neurology* 1979; 29: 1450-1459.
7 Mehrotra TN, Aneja GK, Arora V, et al. Valproate sodium in epilepsy. A clinical trial including monitoring of drug levels. *J Assoc Physicians India* 1990; 38: 277-279.
8 Gram L, Flachs H, Würtz-Jørgensen A, et al. Sodium valproate, serum level and clinical effect in epilepsy: a controlled study. *Epilepsia* 1979; 20: 303-311.
9 Ishikawa T, Ogino C, Furuyama M, et al. Serum valproate concentrations in epileptic children with favourable responses. *Brain Dev* 1987; 9: 283-287.
10 Lundberg B, Nergardh A, Boreus LO. Plasma concentrations of valproate during maintenance therapy in epileptic children. *J Neurol* 1982; 228: 133-141.
11 Jannuzzi G, Cian P, Fattore C, et al. A multicentre randomised controlled trial on the clinical impact of therapeutic drug monitoring in patients with newly diagnosed epilepsy. The Italian TDM Study Group in Epilepsy. *Epilepsia* 2000; 41: 222-230.
12 Scottish Intercollegiate Guideline Network. Diagnosis and management of epilepsy in adults. A national clinical guideline. Guideline No. 70. Edinburgh: SIGN, 2003. http://www.sign.ac.uk/pdf/sign70.pdf (accessed Aug 2007).
13 Eadie MJ. Indications for plasma drug monitoring in patients with epilepsy. Implications for reducing costs. *Pharmacoeconomics* 1997; 11: 343-349.
14 Bowden CL, Janicak PG, Orsulak P, et al. Relation of serum valproate concentration to response in mania. *Am J Psychiatry* 1996; 153: 765-770.
15 Larkin JG, Herrick AL, McGuire GM, et al. Antiepileptic drug monitoring at the epilepsy clinic: a prospective evaluation. *Epilepsia* 1991; 32: 89-95.
16 Schoenenberger RA, Tanasijevic MJ, Jha A, Bates DW. Appropriateness of antiepileptic drug level monitoring. *JAMA* 1995; 274: 1622-1626.
17 Sharpe PC, Morrow J, Trimble ER. An audit of therapeutic drug monitoring of anticonvulsants. *Ulster Med J* 1995; 64: 151-156.
18 Thapar A, Richens A, Roland M, et al. Are serum anticonvulsant levels in people with epilepsy appropriately monitored? *J Eval Clin Pract* 2001; 7: 335-338.
19 Affolter N, Krahenbul S, Schlienger RG. Appropriateness of serum level determinations of antiepileptic drugs. *Swiss Med Wkly* 2003; 133: 591-597.
20 Walters RJ, Hutchings AD, Smith DF, Smith PE. Inappropriate requests for serum anti-epileptic drug levels in hospital practice. *QJM* 2004; 97: 337-341.

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