Journal of Clinical Pharmacy and Therapeutics (2005) **30**, 417–421

Special 30th Anniversary paper

COMMENTARY

Valproate: a simple chemical with so much to offer

G. M. Peterson* PhD MBA and M. Naunton† PhD

**Unit for Medication Outcomes Research and Education, School of Pharmacy, University of Tasmania, Hobart, Australia and †Department of Pharmacotherapy and Pharmaceutical Care, University of Groningen, Groningen, The Netherlands*

The debate exists amongst clinical pharmacologists as to unlimited supplies of which drug would be most useful when stranded on a deserted island. The tricyclic antidepressants have always rated highly because of their variety of useful therapeutic effects, but valproate also deserves to be high on the list. Of course, it will protect against seizures, if they arise, but it could also be useful for analgesia, preventing migraine and stabilizing the mood particularly if one becomes mentally unbalanced on the island. It might even help to prevent the development of cancer.

It would not be an overstatement to suggest that valproate is truly a remarkable drug – a multitude of therapeutic effects from such a simple chemical structure (2-propylpentanoic acid; Fig. 1) – with a remarkable story; it was discovered by chance and is now well-established in the management of a number of neurological conditions and psychiatric disorders. An American chemist (Burton) first synthesized valproate as an organic solvent in 1882 (1). It is a clear, colourless to pale yellow liquid at room and body temperature, and only slightly soluble in water, but highly soluble in organic solvents. The current generic name (valproic acid) was derived from the more descriptive name 2-propylvaleric acid (2).

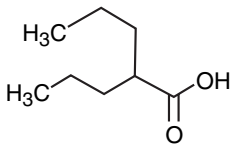

Fig. 1. Chemical structure of valproic acid.

Received 9 May 2005, Accepted 19 May 2005
Correspondence: Gregory Peterson, Unit for Medication Outcomes Research and Education, School of Pharmacy, University of Tasmania, Locked Bag 26, Hobart TAS 7001, Australia. Tel.: 61 3 62262197; fax: 61 3 62267627; e-mail: g.peterson@utas.edu.au

Valproate had been used infrequently as a solvent until its therapeutic properties were serendipitously discovered in 1962 by French researchers, when it was being used as a solvent for other compounds (khelline derivatives) that were being tested for potential anticonvulsant activity (2–4). Eynard and colleagues had encountered difficulty in dissolving some of the derivatives in water or common organic solvents. Valproate was then used to solubilize these compounds and anticonvulsant activity was subsequently observed for the entire test compounds at all doses. Laboratory studies demonstrated anti-seizure activity with valproate (5) and the first clinical trial in epilepsy using the sodium salt of valproic acid was reported in 1964 (6, 7). It was released in France in 1967 (as 'Depakine'), in Great Britain in 1973 and was approved by the US Food and Drug Administration (FDA) in 1978. It was the only new anticonvulsant drug marketed for many years, beforehand and afterwards.

Valproate is currently marketed in over 100 countries and is well established as a first-line and widely used antiepileptic agent, with a very broad spectrum of activity against both generalized and partial seizures in adults and children (4, 8, 9). It is effective against absences and myoclonic, and generalized tonic-clonic seizures. In addition, the drug is useful in the treatment of partial seizures, with or without secondary generalization (2–4, 8, 9). Intravenous valproate has also been shown to be effective against status epilepticus (10).

Results from numerous clinical trials suggest that valproate probably has the widest spectrum of anticonvulsant activity of all current antiepileptic drugs in adults and children with epilepsy (4, 8, 9).

Its mode of action as an anticonvulsant is unclear and might involve several mechanisms (2–4, 8, 9, 11). It has been demonstrated that valproate potentiates γ-aminobutyric acid inhibitory effects in the central nervous system. In addition, valproate might also act through attenuation of N-methyl-D-aspartate receptor-mediated excitation, although this does not explain the effect of valproate on absence seizures (4). It has also been proposed that valproate exerts its effect via blockade of voltage-dependent sodium channels, although this has not been clearly confirmed. Acting to alter the balance of neuronal inhibition and excitation through more than one mechanism is clearly an advantage for an anticonvulsant and is likely to contribute to its broad spectrum of clinical effects (4).

Valproate also possesses an impressive safety profile, being well-tolerated in most patients (4, 9, 12). Most adverse effects are mild to moderate in intensity and hypersensitivity reactions are rare. Valproate causes fewer neurological adverse effects and skin rashes than phenytoin or barbiturates, and its tolerability and safety appear to be similar to that of carbamazepine (4). The main issues of concern with valproate have been idiosyncratic liver toxicity, haematological toxicity and teratogenicity. Recently, valproate has been shown to exert deleterious effects on markers of bone turnover (13) and bone mineral density (14, 15), which might increase the risk of fractures in long-term users (16), although this requires further study. Weight gain is a frequently encountered problem (17, 18).

Transient elevations of liver enzymes without clinical symptoms are seen in 15–30% of patients treated with valproate (19). In contrast, valproate-induced hepatotoxicity is rare, but often fatal. It occurs most frequently in children under 2 years of age and those taking multiple drugs. The overall incidence is one in 20 000, but there is a frequency as high as one in 600 or one in 800 in high-risk groups such as infants >2 years of age receiving anticonvulsant polytherapy (8).

The liver metabolism of valproate is complex and involves microsomal oxidation and glucuronidation (CYP2C9, CYP2C19 and CYP2A6). At least 10 metabolites have been identified (9, 12, 20). The hepatotoxicity of valproate is most likely associated with accumulation of 2,4-diene-valproate and/or 4-ene-valproate (19) and is because of the direct disruption of mitochondrial processes, perhaps through drug-induced carnitine deficiency (21). Cases usually present with non-specific symptoms such as lethargy, nausea/vomiting, or worsening seizures and there is a rapid progression to coma. Liver histopathology is characterized by steatosis with and without necrosis of hepatocytes.

Apart from the multiple metabolic pathways of elimination, the pharmacokinetics of valproate are characterized by excellent but dose-limited absorption and non-linear plasma protein binding (12). In the management of epilepsy, valproate has an accepted therapeutic range of total plasma concentrations of 300–600 μM (50–100 mg/L) that is relatively wide and should be seen more of a guide rather than a clear-cut range (22, 23).

Clinically significant drug interactions involving valproate are also uncommon – the most important being the inhibition of the metabolism of lamotrigine (24, 25), increasing the risk of rash and Stevens–Johnson syndrome (26–28).

In recent times, the use of valproate has spread to a range of other indications, including psychiatric disorders, migraine prophylaxis and the management of trigeminal or post-herpetic neuralgia (29–33).

The first anecdotal evidence that valproate might be useful in migraine sufferers arose in patients with coexisting migraine and epilepsy (2). Positive results in a number of clinical trials subsequently lead to FDA approval for migraine in 1996 (34–36). There is also recent evidence that intravenous valproate (500–800 mg) is effective and well-tolerated in the treatment of acute migraine attacks (37, 38).

Lambert first reported efficacy of valproate in bipolar disorder in 1966 (39). A series of open and small crossover placebo-controlled studies followed over the next 15 years, all with generally positive results and most indicating high rates of response in mania and lower rates of response in depression (40). According to Bowden and Singh (41), valproate has had the largest impact of any drug on changes in treatment approaches to bipolar disorder over the past decade.

Valproate has also been used as treatment for alcohol withdrawal and dependence and reduction of cocaine use (42), as an adjunctive agent for the treatment of schizophrenia (43), tardive dyskinesia (44), agitation associated with late-life psychosis and Alzheimer's disease, and borderline personality disorder (32, 33, 45, 46).

The first reports of toxic effects to the embryo in pregnant epileptic women treated with valproate were published in 1982 (47). Valproate has since been associated with a variety of major and minor foetal malformations, including a 20-fold increase in neural tube defects (1–3% risk), cleft lip and palate, cardiovascular abnormalities, genitourinary defects, developmental delay, endocrinological disorders, limb defects and autism (48). It has been suggested that polytherapy treatment in epileptic pregnant women increases the risk of teratogenicity. There is a dose–effect relationship for foetal malformations and exposure to valproate during the first trimester of pregnancy, with higher doses of valproate associated with a significantly greater risk than with lower doses or with other anticonvulsant drugs (48, 49).

It has become evident that some of the mechanisms that account for the foetal malformations produced by valproate are related to distinct antitumor properties of this drug. *In vitro* models that were established to investigate the teratogenicity of valproate fortuitously identified that valproate possessed anti-proliferative effects and reduced cell growth (50, 51). This intriguing discovery opens novel aspects for the treatment of patients with cancer (50–52). Valproate has been found to exert an anti-proliferative effect on certain cancer cell lines both *in vitro* and *in vivo*, and there are now preliminary reports of the use of valproate in human haematological and solid tumours (52). Clinical studies are underway and the preliminary results indicate that valproate alone or in combination offers a promising avenue of treatment, both in solid and haematopoetic malignancies (51).

In light of the hepatotoxicity and teratogenicity associated with valproate, there is ongoing intensive research to develop new, safer analogues of valproate. Amide derivatives of valproate have shown particular value as potential follow-up compounds. These include valproyl glycinamide, 3-methylbutanamide or isovaleramide and SPD421 (DP-valproate) (53, 54).

Valproate has progressed from being a serendipitous discovery to become a first-line therapy for many forms of epilepsy. Its use has spread to now include migraine prophylaxis and management of bipolar disorder. Future developments are likely to further improve its efficacy and tolerability. More clinical uses will also undoubtedly appear for this fascinating molecule.

REFERENCES

1. Burton BS (1882) On the propyl derivatives and decomposition products of ethylacetoacetate. *Journal of American Chemistry*, **3,** 385–395.
2. Henry TR (2003) The history of valproate in clinical neuroscience. *Psychopharmacology Bulletin*, **37**(Suppl. 2)**,** 5–16.
3. Johannessen CU, Johannessen SI (2003) Valproate: past, present, and future. *CNS Drug Reviews*, **9,** 199–216.
4. Löscher W (2002) Basic pharmacology of valproate: a review after 35 years of clinical use for the treatment of epilepsy. *CNS Drugs*, **16,** 669–694.
5. Meunier H, Carraz G, Neunier Y, Eymard P, Aimard M (1963) Pharmacodynamic properties of N-dipropylacetic acid. *Therapie*, **18,** 435–438.
6. Carraz G, Fau R, Chateau R, Bonnin J (1964) Communication concerning 1st clinical tests of the anticonvulsive activity of N-Dipropylacetic Acid (sodium salt). *Annales Medico-Psychologiques*, **122,** 577–585.
7. Lebreton S, Carraz G, Meunier H, Beriel H (1964) Pharmacodynamic properties of 2,2-dipropylacetic acid. 2nd report on its anti-epileptic properties. *Therapie*, **19,** 451–456.
8. Perucca E (2002) Pharmacological and therapeutic properties of valproate: a summary after 35 years of clinical experience. *CNS Drugs*, **16,** 695–714.
9. Davis R, Peters DH, McTavish D (1994) Valproic acid. A reappraisal of its pharmacological properties and clinical efficacy in epilepsy. *Drugs*, **47,** 332–372.
10. Peters CN, Pohlmann-Eden B (2005) Intravenous valproate as an innovative therapy in seizure emergency situations including status epilepticus – experience in 102 adult patients. *Seizure*, **14,** 164–169.
11. Löscher W (1999) Valproate: a reappraisal of its pharmacodynamic properties and mechanisms of action. *Progress in Neurobiology*, **58,** 31–59.
12. DeVane CL (2003) Pharmacokinetics, drug interactions, and tolerability of valproate. *Psychopharmacology Bulletin*, **37**(Suppl. 2)**,** 25–42.
13. Pack AM, Morrell MJ, Marcus R *et al*. (2005) Bone mass and turnover in women with epilepsy on antiepileptic drug monotherapy. *Annals of Neurology*, **57,** 252–257.
14. Sato Y, Kondo I, Ishida S *et al*. (2001) Decreased bone mass and increased bone turnover with valproate therapy in adults with epilepsy. *Neurology*, **57,** 445–449.

15. Ecevit C, Aydogan A, Kavakli T, Altinoz S (2004) Effect of carbamazepine and valproate on bone mineral density. *Pediatric Neurology*, **31,** 279–282.
16. Vestergaard P, Rejnmark L, Mosekilde L (2004) Fracture risk associated with use of antiepileptic drugs. *Epilepsia*, **45,** 1330–1337.
17. Pijl H, Meinders AE (1996) Bodyweight change as an adverse effect of drug treatment. Mechanisms and management. *Drug Safety*, **14,** 329–342.
18. Biton V (2003) Effect of antiepileptic drugs on bodyweight: overview and clinical implications for the treatment of epilepsy. *CNS Drugs*, **17,** 781–791.
19. Anderson GD (2002) Children versus adults: pharmacokinetic and adverse-effect differences. *Epilepsia*, **43**(Suppl. 3), 53–59.
20. Zaccara G, Messori A, Moroni F (1988) Clinical pharmacokinetics of valproic acid – 1988. *Clinical Pharmacokinetics*, **15,** 367–389.
21. Bohan TP, Helton E, McDonald I *et al*. (2001) Effect of L-carnitine treatment for valproate-induced hepatotoxicity. *Neurology*, **56,** 1405–1409.
22. Eadie MJ (2001) Therapeutic drug monitoring – antiepileptic drugs. *British Journal of Clinical Pharmacology*, **52**(Suppl. 1), S11–S20.
23. Chadwick DW (1985) Concentration–effect relationships of valproic acid. *Clinical Pharmacokinetics*, **10,** 155–163.
24. Yuen AW, Land G, Weatherley BC, Peck AW (1992) Sodium valproate acutely inhibits lamotrigine metabolism. *British Journal of Clinical Pharmacology*, **33,** 511–513.
25. Riva R, Albani F, Contin M, Baruzzi A (1996) Pharmacokinetic interactions between antiepileptic drugs. Clinical considerations. *Clinical Pharmacokinetics*, **31,** 470–493.
26. Famularo G, De Simone C, Minisola G (2005) Stevens–Johnson syndrome associated with single high dose of lamotrigine in a patient taking valproate. *Dermatology Online Journal*, **11,** 25.
27. Huang CW, Tsai JJ, Lai ML (2002) Lamotrigine-related skin rashes in adults. *The Kaohsiung Journal of Medical Sciences*, **18,** 566–572.
28. Guberman AH, Besag FM, Brodie MJ *et al*. (1999) Lamotrigine-associated rash: risk/benefit considerations in adults and children. *Epilepsia*, **40,** 985–991.
29. Spina E, Perugi G (2004) Antiepileptic drugs: indications other than epilepsy. *Epileptic Disorders*, **6,** 57–75.
30. Sindrup SH, Jensen TS (2002) Pharmacotherapy of trigeminal neuralgia. *Clinical Journal of Pain*, **18,** 22–27.
31. Kochar DK, Garg P, Bumb RA, Kochar SK, Mehta RD, Beniwal R, Rawat N (2005) Divalproex sodium in the management of post-herpetic neuralgia: a randomized double-blind placebo-controlled study. *QJM: Monthly Journal of the Association of Physicians*, **98,** 29–34.
32. Davis LL, Ryan W, Adinoff B, Petty F (2000) Comprehensive review of the psychiatric uses of valproate. *Journal of Clinical Psychopharmacology*, **20**(Suppl. 1), S1–S17.
33. Tariot PN (2003) Valproate use in neuropsychiatric disorders in the elderly. *Psychopharmacology Bulletin*, **37**(Suppl. 2), 116–128.
34. Jensen R, Brinck T, Olesen J (1994) Sodium valproate has a prophylactic effect in migraine without aura: a triple-blind, placebo-controlled crossover study. *Neurology*, **44,** 647–651.
35. Hering R, Kuritzky A (1992) Sodium valproate in the prophylactic treatment of migraine: a double-blind study versus placebo. *Cephalalgia*, **12,** 81–84.
36. Rothrock JF (1997) Clinical studies of valproate for migraine prophylaxis. *Cephalalgia*, **17,** 81–83.
37. Leniger T, Pageler L, Stude P, Diener HC, Limmroth V (2005) Comparison of intravenous valproate with intravenous lysine-acetylsalicylic acid in acute migraine attacks. *Headache*, **45,** 42–46.
38. Edwards KR, Norton J, Behnke M (2001) Comparison of intravenous valproate versus intramuscular dihydroergotamine and metoclopramide for acute treatment of migraine headache. *Headache*, **41,** 976–980.
39. Lambert PA, Carraz G, Borselli S, Carbel S (1966) Neuropsychotropic action of a new anti-epileptic agent: depamide. *Annales Medico Psychologiques*, **124,** 707–710.
40. Bowden CL (2003) Valproate. *Bipolar Disorder*, **5,** 189–202.
41. Bowden CL, Singh V (2005) Valproate in bipolar disorder: 2000 onwards. *Acta Psychiatrica Scandinavica. Supplementum*, **426,** 13–20.
42. Zullino DF, Khazaal Y, Hattenschwiler J, Borgeat F, Besson J (2004) Anticonvulsant drugs in the treatment of substance withdrawal. *Drugs Today*, **40,** 603–619.
43. Citrome L (2003) Schizophrenia and valproate. *Psychopharmacology Bulletin*, **37**(Suppl. 2), 74–88.
44. Soares KV, McGrath JJ (1999) The treatment of tardive dyskinesia – a systematic review and meta-analysis. *Schizophrenia Research*, **39,** 1–16.
45. Salzman C (2001) Treatment of the agitation of late-life psychosis and Alzheimer's disease. *European Psychiatry*, **16**(Suppl. 1), S25–S28.
46. Devanand DP (1997) Behavioral complications and their treatment in Alzheimer's disease. *Geriatrics*, **52**(Suppl. 2), S37–S39.
47. Bjerkedal T, Czeizel A, Goujard J *et al*. (1982) Valproic acid and spina bifida. *Lancet*, **2,** 1096.

48. Alsdorf R, Wyszynski DF (2005) Teratogenicity of sodium valproate. *Expert Opinion Drug Safety*, **4,** 345–353.
49. Vajda FJ, O'Brien TJ, Hitchcock A *et al*. (2004) Critical relationship between sodium valproate dose and human teratogenicity: results of the Australian register of anti-epileptic drugs in pregnancy. *Journal of Clinical Neuroscience*, **11,** 854–858.
50. Blaheta RA, Nau H, Michaelis M, Cinatl J Jr (2002) Valproate and valproate-analogues: potent tools to fight against cancer. *Current Medicinal Chemistry*, **9,** 1417–1433.
51. Blaheta RA, Michaelis M, Driever PH, Cinatl J Jr (2005) Evolving anticancer drug valproic acid: Insights into the mechanism and clinical studies. *Medicinal Research Reviews*, **25,** 383–397.
52. Singh G, Driever PH, Sander JW (2005) Cancer risk in people with epilepsy: the role of antiepileptic drugs. *Brain*, **128,** 7–17.
53. Isoherranen N, Yagen B, Bialer M (2003) New CNS-active drugs which are second-generation valproic acid: can they lead to the development of a magic bullet? *Current Opinion in Neurology*, **16,** 203–211.
54. Trojnar MK, Wierzchowska-Cioch E, Krzyzanowski M, Jargiello M, Czuczwar SJ (2004) New generation of valproic acid. *Polish Journal of Pharmacology*, **56,** 283–288.