Structure–Pharmacokinetic Relationships in a Series of Valpromide Derivatives with Antiepileptic Activity

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The following valpromide (VPD) derivatives were synthesized and their structure–pharmacokinetic relationships explored: ethylbutyrlacetamide (EBD), methylpentylacetamide (MPD), propylisopropylacetamide (PID), and propylallylacetamide (PAD). In addition, the anticonvulsant activity of these compounds was evaluated and compared to that of VPD, valnoctamide (VCD), and valproic acid (VPA). MPD, the least-branched compound had the largest clearance and shortest half-life of all the amides investigated and was the least active. All other amides had similar pharmacokinetic parameters. Unlike the other amides, PID and VCD did not metabolize to their respective homologous acids and were the most active compounds. Our study showed that these amides need an unsubstituted $\beta$ position in their aliphatic side chain in order to biotransform to their homologous acids. An amide which is not metabolized is more potent as an anticonvulsant than its biotransformed isomer. All amides were more active than their respective homologous acids. In this particular series of aliphatic amides, which were derived from short-branched fatty acids, the anticonvulsant activity was affected by the pharmacokinetics in general and by the biotransformation of the amide to its homologous acid in particular. This amide–acid biotransformation appeared to be dependent upon the chemical structure, especially upon the substitution at position $\beta$ of the molecule.

KEY WORDS: valpromide; valproic acid; antiepileptic activity; SAR; pharmacokinetics.

Introduction

Valpromide or dipropylacetamide (VPD-I; Fig. 1), a primary amide of valproic acid, is widely used in several European countries, both as an antiepileptic and as an antipsychotic drug (1–3).

Previous reports (3–5) have shown that, upon oral administration to humans, valpromide was biotransformed to valproic acid (VPD-II; Fig. 1), a well-known antiepileptic agent (6), before reaching the systemic circulation. Pharmacokinetic analysis demonstrated that VPD is a prodrug of VPA (2–5,7,8) and that this may account for its antiepileptic activity.

Loscher and Nau (9) reported that among a series of VPA analogues tested in mice for anticonvulsant activity, VPD was found to be the most potent, being two to five times more potent than VPA. However, VPD also exerted a more significant sedative side effect. Recent articles have reported that VPD also possesses specific properties of its own (unrelated to VPA), i.e., the induction of an elevation in the plasma levels of carbamazepine-10,11-epoxide, the active metabolite of carbamazepine (10–14).

Following i.v. administration, VPD was shown to be rapidly and almost completely metabolized to VPA in humans, with an $f_m$ value of 80% ($f_m$ = the metabolized fraction of VPD to VPA) (8). In dogs, VPD’s biotransformation to VPA was only partial and was independent of the route of administration, the $f_m$ being in the range of 30–40% (15,16).

Valnoctamide (VCD-III; Fig. 1; valmethamide or 2-ethyl-3-methylpentamide), an isomer of VPD, has also proven useful as a tranquilizer in the treatment of anxiety and tension (17–19). In a recent study in dogs, it was reported that VCD’s major pharmacokinetic parameters were similar to those of VPD (20), the main difference being that VCD was not a prodrug of its homologous acid (valnoctic acid; VCA-IV; Fig. 1). This pharmacokinetic (or metabolic) difference may explain the different pharmacological properties of the two isomers. The extent of biotransformation of an aliphatic amide (such as VPD or VCD) to its homologous acid, therefore, appears to be a key issue in these compounds’ pharmacological activity.

Another compound, similar to both VPD and VCD, is allylisopropylacetamide (AIA-V; Fig. 1). In contrast to VPD and VCD, which are used as drugs, AIA is defined as a “suicide substrate” (21,22). Despite the fact that VPD, VCD, and AIA are chemically similar, there are marked differences in their pharmacological properties.

Keane et al. (23) and Loscher and Nau (9) have demonstrated that within a large series of branched monocarboxylic acids, VPA had the optimal chemical structure with regard to margins between its anticonvulsant effect and its sedative/hypnotic side effects. Since pharmacokinetics plays a major role in the pharmacological activity of these ali-

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appropriate alkyl halide (all chemicals were purchased from Aldrich, Milwaukee, Wis.). The acids were then obtained by decarboxylation (heating to 150–180°C until the elaboration of all of the CO₂ stopped) of the condensation product and the amides (compounds VI to IX) by amidation of the acyl chloride with ammonia. The chemical structures were confirmed by nuclear magnetic resonance (NMR) and elementary microanalysis.

Animals

The experiments were carried out in six dogs (mongrels), three males and three females, ranging in weight between 18 and 23 kg. Although mice and rats are usually used for anticonvulsant screening (24), these animals are too small to be used in pharmacokinetic studies with a crossover design. In addition, the disposition of drugs in dogs has the potential of being more similar to that in humans than the disposition of the same drugs in rodents. In a randomized crossover design, each dog was injected intravenously with 400 mg (in 1.5 ml 70% alcohol) of the amide (into one of the cephalic veins). In cases where an amide was biotransformed into its homologous acid, the acid was also administered (i.v., 400 mg). Urine was collected systematically for 16 hr from all dogs by means of an indwelling catheter. A washout period of 3 weeks was allowed between any two consecutive studies.

Protocol

Venous blood samples (6 ml) were collected via an indwelling catheter (the other cephalic vein) at specified intervals following injection (0, 2, 5, 10, 15, 20, 30, 40, and 50 min and 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, and 10 hr, respectively). The plasma was then immediately separated by centrifugation at 7000 rpm for 15 min and stored at –20°C. Before each assay, the plasma was allowed to reach room temperature, vortexed, and centrifuged, and the residual clot removed. Plasma levels of the amide and its homologous acid were assayed by gas–liquid chromatography (GLC), an assay which we have reported on for the determination of VPD and VCD (25,26).

As the acids of compounds VI to IX were considered, a priori, to be potential metabolites of the amides, they were also synthesized. In preliminary studies we verified the fact that the acids can also be detected and monitored, simultaneously with the appropriate amide, in our GLC assay.

Anticonvulsant Activity

The amides VPD (I), VCD (III), EBD (VI), MPD (VII), PID (VIII), and PAD (IX) and their respective homologous acids were screened in mice for their anticonvulsant activity by the NIH Epilepsy Branch (24). The screening procedure involved the following: (i) the maximal electroshock (MES) test, which measures seizure spread; (ii) the subcutaneous pentylentetrazol test (s.c. Met. test), which measures seizure threshold; and (iii) the rotorod ataxia test, which assesses neurotoxicity.

Pharmacokinetic Analysis

The linear terminal slope (β) of log C (amide or acid

Fig. 1. Chemical structures of the different aliphatic amides and acids discussed in the paper.

phatic amides, we decided to explore the structure–pharmacokinetic relationships that may exist within a series of VPD (or VCD) isomers or derivatives which contain eight carbon atoms per molecule.

The following aliphatic branched-chain amides were synthesized and their pharmacokinetics investigated in dogs (following i.v. administration): ethylbutylacetamide (EBD-VI), methylpentylacetamide (MPD-VII), propylisopropylacetamide (PID-VIII), and propylallylaceticamide (PAD-IX). The chemical structures of these amides are depicted in Fig. 1.

In order to evaluate whether any relationships exist among chemical structure, pharmacokinetics, and anticonvulsant activity in the above-mentioned compounds, we tested and evaluated the antiepileptic data of our compounds by using the anticonvulsant screening project of the NIH Epilepsy Branch (24).

MATERIALS AND METHODS

Materials

The amides (compounds VI to IX) and their homologous acids were synthesized by means of the classical method of a condensation between the diethylmalonate ester and the