Intravenous (i.v.) administration of antiepileptic drugs (AEDs) produces the most rapid onset of action, as it is delivered directly into the bloodstream and immediately produces maximal plasma concentration ($C_0 = C_{max}$). In addition to its therapeutic value, i.v. administration is essential in investigating the pharmacokinetics (PK) or clinical pharmacology of drugs, as it bypasses absorption and focuses on the disposition (distribution plus elimination) of drugs. Consequently due to its direct delivery of drugs to the blood, i.v. injection or infusion is the reference route for absolute bioavailability calculations.

Other parenteral routes like intramuscular (im) or subcutaneous (sc) administration are examples of extravascular (ev) administration involving absorption processes and therefore, drug plasma profiles produced are similar to the one obtained following oral administration of conventional (immediate release) formulations. Most AEDs exhibit linear (concentration-independent) PK and therefore their major PK parameters: clearance (CL), apparent volume of distribution (V), and half-life ($t_{1/2}$) are not affected by the route of administration or by the rate or extent of absorption (Bialer and Cloyd, 1995). Changes in route of administration or in the parenteral (ev) formulation only affect the extent and rate of absorption, whereas the disposition is an intrinsic property of the AED or the active entity.

Similar to oral formulations, parenteral preparations intended for im or sc injections may be formulated to have a rapid or slow rate of absorption. The preferred parenteral preparations are aqueous solutions that generally distribute rapidly from the administration site. Hydroalcoholic, oily, or suspension vehicles may result in slow and sustained absorption, side effect of the nonaqueous solvents (e.g., propylene glycol) and unlike aqueous injections cannot be diluted for infusions. The differences between aqueous and hydroalcoholic parenteral preparations of AEDs are best illustrated in the development of fosphenytoin.

Fosphenytoin is a disodium phosphate ester of 3-hyroxymethyl of phenytoin developed as a replacement for standard injectable phenytoin sodium. The water solubility of fosphenytoin is 75,000 mg/L versus only 20 mg/L for phenytoin sodium. Consequently, fosphenytoin was designed and developed as an aqueous injectable phenytoin prodrug to avoid the local complications associated with parenteral phenytoin such as i.v. fluid incompatibilities, patient discomfort, vein irritation/tissue damage, and muscle necrosis after im administration. The parenteral preparation of phenytoin sodium is a hydroalcoholic mixture of 40% propylene glycol, 10% alcohol, and 50% water with the pH adjusted to 12, necessary to provide 50 mg/ml solution of sodium phenytoin, while fosphenytoin is an aqueous solution. Fosphenytoin is administered either by i.v. or im route and is rapidly and completely converted enzymatically to phenytoin (conversion $t_{1/2} = 3$ min in dogs, 1 min in rats) (Browne & LeDuc, 1995). Admixtures of fosphenytoin solutions diluted to phenytoin concentrations of 1, 8, and 20 mg/ml in 0.9% NaCl, D5W, and other 11 i.v. fluids were physically compatible and chemically stable. Clinical studies in adults and children indicate that im and i.v. of fosphenytoin were well tolerated, safe and rapidly and completely converted to phenytoin (Bialer et al., 2002).

Sodium valproate injection (Depacon) was approved in the United States in 1996 for intravenous use in epileptic patients for whom oral administration of VPA is temporarily not feasible. At a median dose of 375 mg administered over 1 h infusion, sodium valproate was safe and well tolerated in 318 patients hospitalized for seizures (Devinsky et al., 1995; Bialer et al., 2004). Naritoku and Mueed demonstrated the safety of an i.v. (loading) dose of sodium valproate when a rapid increase in VPA serum level was required to stop recurrent seizures. A mean dose of 19.4 mg/kg infused at 20 and 50 mg/min in 0.9% NaCl, D5W, and other 11 i.v. fluids were physically compatible and chemically stable. Clinical studies in adults and children indicate that im and i.v. of fosphenytoin were well tolerated, safe and rapidly and completely converted to phenytoin (Bialer et al., 2002).

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peak plasma concentration was 94 mg/L and fell below 50
mg/L within 3 h in induced and 6 h in noninduced patients. 
VPA mean (SD) volume of distribution was 0.21 (0.044)
L/kg and its fraction unbound to plasma albumin decreased
from 15% at 94 mg/L to 9% at 45 mg/L. The authors con-
cluded that VPA infusions of up to 3 mg/kg/min produce
predictable total VPA concentrations when induction sta-
tus and albumin levels are considered. Ramsay et al. eval-
uated the safety of sodium valproate infusion utilizing as a
primary safety endpoint the changes in the 5-min and min-
imum post first infusion blood pressure. They concluded
that i.v. dosages up to 15 mg/kg given at rates of 1.5
and 3.0 mg/kg/min were well tolerated in this patient popu-
lation (Ramsay et al., 2003). Recently, Limdi et al. demon-
strated that rapid administration of undiluted Depacon was
safe and well tolerated infusion rate up to 10 mg/kg/min
doses up to 30 mg/kg (Limdi et al., 2007).

Carbamazepine (CBZ), a neutral water-insoluble com-
ound, presents difficulties when formulating it in a
parenteral preparation. However, the water solubility of
CBZ can be greatly enhanced by solubilizing it in (or
forming a complex with) the cyclodextrin derivative, 2-
hydroxypropyl-ß-cyclodextrin (Loscher et al., 1995). Stud-
ies in dogs indicated that i.v. administration of the CBZ
cyclodextrin complex was well tolerated. Ovation Phar-
maceuticals is currently conducting clinical trials with a
patent-protected i.v. formulation of CBZ (i.v. CBZ) to char-
acterize the pharmacokinetics of CBZ after i.v. adminis-
tration and to provide a consistent transition therapy for
patients on oral CBZ (Collins, 2007). The primary objec-
tives of these studies are: (a) to assess the safety and tol-
erability of i.v. CBZ given as an i.v. infusion over 15
and 30 min; (b) to compare the pharmacokinetics of CBZ fol-
lowing repetitive i.v. dosing (7 days) at steady-state to that
obtained after a single oral dose. The secondary objectives
are to assess the pharmacokinetics, safety, and tolerability
of i.v. CBZ following rapid i.v. infusion (2 and 5 min) and
in patients with mild or moderate impairments (Collins,
2007). CBZ i.v. formulations offer valuable, short-term
treatment options for patients scheduled for surgery and
for patients who cannot be treated with oral CBZ due to
emergency situations, loss of consciousness, or GI distur-
bances. Finally, such parenteral preparations could prove
useful in acute, critical care situations such as status epilep-
ticus (SE).

The goals of pharmacological therapy of SE are to
terminate seizures early and prevent recurrence. Two re-
cent large clinical studies have shown the benefit of early
administration of benzodiazepines to control SE. New
AEDs have provided alternatives to the traditional treat-
ment paradigms for SE. However, most new AEDs are still
not available in a parenteral formulation and thus cannot be
utilized in the treatment of SE. The first line drugs are the
benzodiazepines: lorazepam and diazepam that are used
for the initial treatment of SE. Diazepam achieves high
brain concentrations and has a slightly faster onset of ac-
tion. However, diazepam redistributes rapidly to peripheral
fats and consequently its clinical effectiveness is limited
to 20–30 min. Therefore, diazepam treatment of SE needs
to be followed with a second drug such as lorazepam. Lo-
razepam has a more favorable pharmacokinetic profile than
diazepam and its duration of action exceeds 12 h.
Phenytoin or its parenteral prodrug fosphenytoin are also
utilized in the treatment of SE with a loading dose of 1 g
or 20 mg/kg administered at a maximal rate of 50 mg/min.
In the absence of clinical effect, an additional 10 mg/kg
is given because many patients may require PHT plasma
levels of 25–30 mg/L to achieve seizure control. The most
common side effects of PHT i.v. dosing are cardiovascular
including hypotension and QT prolongation. Phenobarbi-
tal has been shown to be effective for the treatment of SE,
but it is considered a third-line drug in the algorithms de-
dsigned to treat SE because of its serious adverse effect pro-
file. Phenobarbital’s long half-life and the presence of an
active metabolite are drawbacks in terms of adverse effects.
Although treatment of SE with VPA holds promise, the ex-
perience with VPA in the treatment of SE has been limited
to several small studies. VPA’s main advantage over other
AEDs appears to be its safety profile and ease of adminis-
tration.

An i.v. formulation of levetiracetam has been developed
and was found to be bioequivalent to the commercially
available oral formulation of levetiracetam (Ramel, 2006a).
The recommended dose of 1,000–3,000 mg/day must be
diluted in >100 ml compatible diluents (e.g., 0.9% NaCl,
D5W) and administered as a 15-min infusion. This formu-
lation has been approved in the European Union and by
the FDA (Bialer et al., 2007). Intravenous levetiracetam
appears to be well tolerated in healthy adults even at fast
infusion rates (1,500–2,500 mg administered over 5 min)
and provides a useful alternative for patients unable to take
levetiracetam orally (Baulac, 2005; Ramel, 2006b). A re-
cent study in dogs showed that following i.m. administra-
tion, levetiracetam is rapidly and completely absorbed and
suggested that levetiracetam should be evaluated for i.m
administration to humans (Goel et al., 2006). A recent multi-
center, open-label study evaluated the short-term tolerabil-
ity of a 15-min i.v. infusions of levetiracetam (500–1,500
mg/100 ml, bid) and found that it was well tolerated and
provides a practical alternative in patients with partial on-
set seizures that temporarily are unable to take levetirac-
etam orally (Baulac et al., 2007).

Recently, an i.v. formulation of the water-soluble new
AED lacosamide was developed to facilitate treatment of
patients receiving lacoamside who temporarily become
unable to take oral medications. Intravenous lacosamide
is a stable aqueous solution of the parent compound
(10 mg/ml) that does not require dilution prior to admin-
istration and is intended to deliver 200 mg lacosamide over
30 or 60 min (Krauss et al., 2006). In phase I, clinical
trials lacosamide was well tolerated and the reported adverse events were mostly mild and similar to the ones described for oral lacosamide (Bialer et al., 2004). Bioequivalence has been demonstrated between oral and i.v. infusion (30 and 60 min) of lacosamide. The highest single dose was 300 mg. After i.v. dosing, lacosamide plasma concentration-time curves were similar to those obtained after oral administration and the metabolic profile was comparable to oral dosing (Bialer et al., 2007).

A preliminary report describes the pharmacokinetics of lamotrigine (LTG) following an intravenous administration of stable-labeled LTG formulation (Remmel et al., 2006). Epileptic patients on steady-state maintenance LTG therapy were given a single 50 mg replacement of the \(^{13}C_2, ^{15}N\)-LTG formulation as part of their daily LTG regimen. Five younger women (age 25–48 years) have completed the study. LTG doses ranged from 200 to 800 mg/day. These preliminarily data indicate that the investigated LTG i.v. formulation is safe and well tolerated when administered to relatively healthy adult patients (Remmel et al., 2006).

In conclusion, parenteral formulations of AEDs are quite feasible for AEDs that are water-soluble. In order to be administered in an aqueous injection, water-insoluble AEDs need to be formulated in a chemical drug delivery or a prodrug (e.g., fosphenytoin) or via solubilization in a pharmaceutical drug delivery (e.g., CBZ). Parenteral preparations contribute significantly to the antiepileptic armament and are essential in the treatment of patients who cannot be given AEDs orally. The global sales of fosphenytoin (that is only available parenterally) in 2004 and 2005 were only $63 and $70 millions, respectively, compared to $326 millions, for oral phenytoin (IMS, 2006). Although the market for parenteral AEDs per se is small (as reflected by fosphenytoin), the fact that injectable formulations serve as an introduction for oral medication to which patients will be switched upon release from the hospital, shall serve as an incentive for the pharmaceutical industry to develop parenteral formulations for additional AEDs even if they are water-insoluble compounds.

**REFERENCES**


