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Fospropofol Disodium

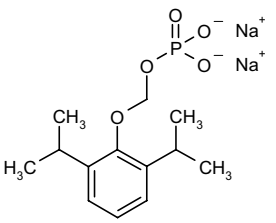
Anesthetic Drug

Prop INNM; USAN

GPI-15715
PQ-1002
Aquavan®

2,6-Diisopropylphenoxymethyl dihydrogenphosphate disodium salt

Phosphoric acid 2,6-diisopropylphenoxymethyl monoester disodium salt



$C_{13}H_{19}Na_2O_5P$
Mol wt: 332.2403

CAS: 258516-87-9

CAS: 258516-89-1 (as free acid)

EN: 285963

Abstract

Fospropofol disodium is a water-soluble prodrug of propofol designed to overcome some of the disadvantages associated with the current lipid-based formulation. Adverse effects associated with the lipid formulation include pain at the site of injection, the potential for hyperlipidemia with long-term administration and an increased potential for bacteremia. Upon injection, propofol is released from the prodrug and equilibrates rapidly into brain tissue to exert a dose-dependent anesthetic effect. Phase I studies have shown that released propofol induces anesthesia with greater potency than lipid-based propofol. It also had a different pharmacokinetic disposition, most notably a longer half-life, a larger volume of distribution and a greater clearance rate. Fospropofol disodium was effective at maintaining sedation in phase II studies of patients undergoing colonoscopy and is currently in phase III studies for sedation in patients requiring colonoscopy, bronchoscopy and minor surgical procedures.

Synthesis

This compound can be obtained by several related ways (Scheme 1):

1) The reaction of 2,6-diisopropylphenol (I) with chloro iodomethane (II) by means of NaH in dimethoxyethane gives *O*-(chloromethyl)-2,6-diisopropylphenol (III), which is condensed with silver dibenzyl phosphate (IV) to yield the triester (V). Finally, this compound is deprotected by hydrogenation with H_2 over Pd/C in THF/water and neutralized with Na_2CO_3 to afford the target disodium salt phosphate monoester (1).

2) The reaction of phenol (I) with chloromethyl methyl sulfide (VI) by means of NaH in HMPA gives 2,6-diisopropyl-*O*-(methylsulfanylmethyl)phenol (VII), which is treated with SO_2Cl_2 in dichloromethane to yield the *O*-(chloromethyl) intermediate (III) (1).

3) The reaction of the *O*-(methylsulfanylmethyl) derivative (VII) with phosphoric acid dibenzyl ester (VIII) by means of NIS in dichloromethane gives the triester intermediate (V) (1).

4) The reaction of phenol (I) with formaldehyde bis(dibenzyloxyphosphono)acetal (IX) by means of NaH in dimethoxyethane gives the triester intermediate (V) (1).

5) The reaction of phenol (I) with dibenzyl chloromethyl phosphate (X) by means of NaOH and tetrabutylammonium bromide (TBAB) in dichloromethane/water gives the triester intermediate (V) (1).

6) The reaction of phenol (I) with bromo chloromethane (XI) by means of NaOH in refluxing THF gives *O*-(chloromethyl)-2,6-diisopropylphenol (III), which is condensed with phosphoric acid by means of TEA in hot acetonitrile and treated with NaOH in water to provide the target disodium salt phosphate monoester (2).

Background

Propofol is a rapid-acting sedative that allows patients to recover quickly, making it particularly suitable for use in minor surgical procedures and biopsies that are carried out in the outpatient setting. It is also used in major

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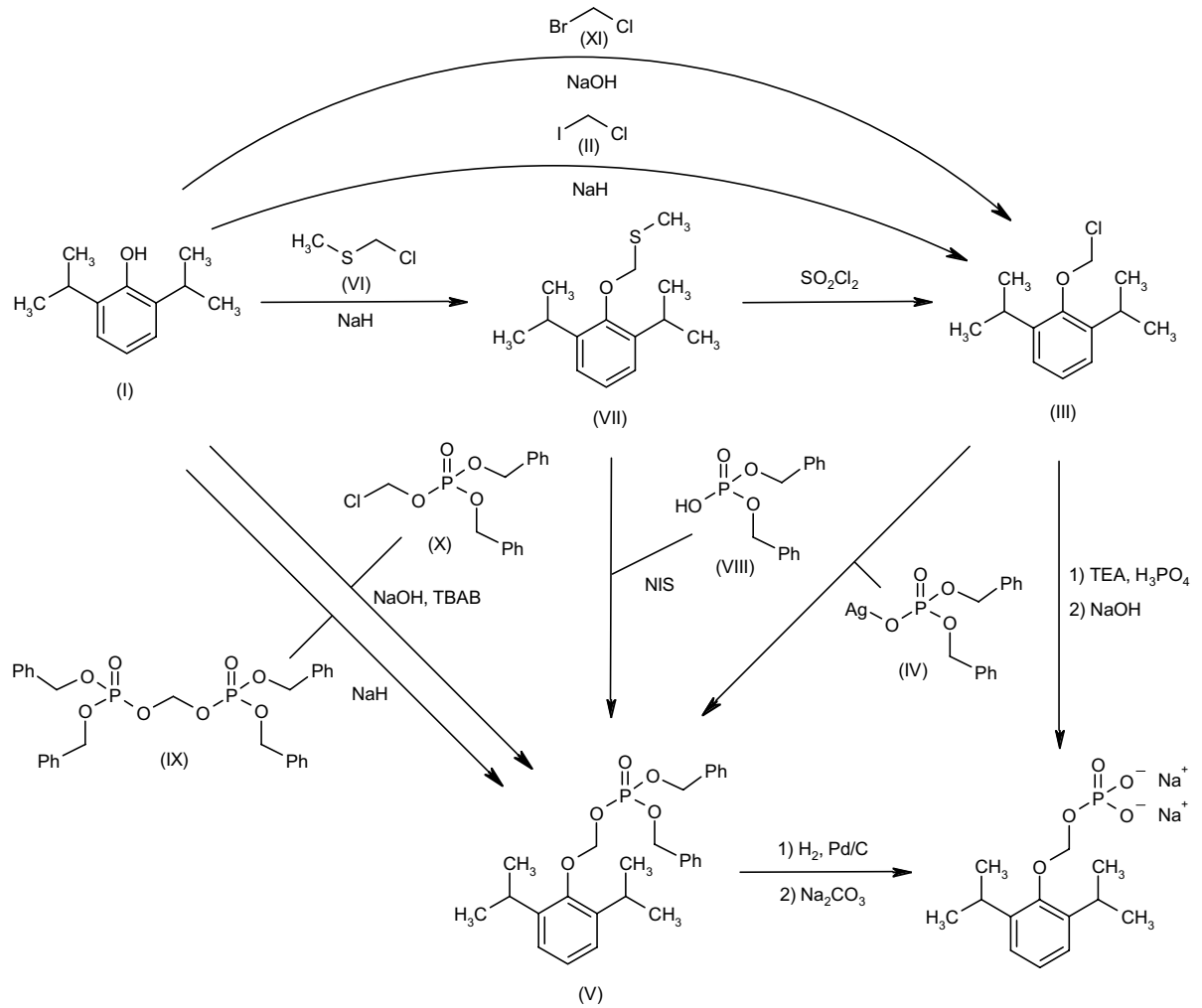
Scheme 1: Synthesis of Fospropofol Disodium



surgical procedures, including cardiac and neurological surgery, and for long-term sedation of critically ill patients in intensive care units (3). Propofol is rapidly metabolized in the liver by conjugation to form inactive glucuronide and sulfate metabolites that are readily secreted by the kidney. A 3-compartment model describes its distribution, with rapid equilibration between the plasma compartment and brain tissue ($t_{1/2}$ = 2-4 min), which accounts for the rapid onset of anesthesia (40 s), and slower equilibration to a peripheral tissue compartment ($t_{1/2}$ = 30-60 min). Propofol has an overall elimination half-life of 4-7 h. The rapid recovery is accounted for by rapid re-equilibration from the brain to other tissues and high metabolic clearance (4).

Propofol is only slightly soluble in water, and although originally formulated in Cremophor EL, it was re-launched in 1986 by Astra Zeneca, under the name Diprivan®, as an emulsion in Intralipid. Adverse effects that are associated with the lipid formulation include pain at the injection site, lipid load and a risk of infection from bacterial contamination and reduced bacterial clearance, and there is some suggestion that the lipid component may exacerbate the hypotension and transient apnea caused by propofol (5-9).

Fospropofol disodium (Aquavan® injection, GPI-15715, PQ-1002) is a water-soluble prodrug of propofol intended to eliminate the disadvantages associated with the current Intralipid-based formulation of propofol. The phosphono-*O*-methyl modification has previously been used successfully to improve the solubility of other medicines, such as the antiepileptic drug phenytoin (fosphenytoin, Cerebyx®, Prodilantin®, Pro-Epanutin®; Pfizer) (10, 11). Upon injection, the prodrug is hydrolyzed by endothelial cell surface alkaline phosphatases to release the active drug propofol, nontoxic inorganic phosphate and formaldehyde. In phase I and II studies, fospropofol disodium was shown to be effective in inducing anesthesia and the drug is currently in phase III studies in patients

undergoing colonoscopy, bronchoscopy and a variety of minor surgical procedures.

Preclinical Pharmacology

Fospropofol disodium sedated rats when administered as a single i.v. bolus injection of 40 mg in saline. Sedation was determined as the mean shift to lower frequencies for > 4 s in the electroencephalogram (EEG) spectrum. The maximum effect on EEG was reached at 7 min, returning to baseline 40 min later, compared to approximately 2 and 25 min, respectively, for commercial propofol. The EC_{50} for released propofol was estimated at 2.6 μg/ml, whereas the EC_{50} for commercial propofol was previously reported to be 4.1 μg/ml, suggesting that propofol released from fospropofol disodium is more potent than propofol in lipid formulation (12).

Pharmacokinetics

Pharmacokinetic analysis in rats administered an i.v. bolus of 40 mg fospropofol disodium in saline showed a C_{max} of 7.1 μg/ml for propofol released from fospropofol disodium, with a time to peak concentration of 3.7 min, reflecting the time required for conversion of the prodrug. The prodrug showed a biphasic decline in plasma concentrations, with half-lives of 2.9 and 23.9 min. The volume of distribution in the plasma was small at 0.25 l/kg, and clearance was rapid at 46.1 ml/kg/min. Propofol released from the prodrug also showed a biphasic decline in plasma concentration, with half-lives of 1.9 and 45 min. The volume of distribution was 2.3 l/kg and clearance was 344 ml/kg/min. Compared to commercial propofol, propofol released from the prodrug had a longer elimination half-life, a larger volume of distribution and a higher clearance rate (12).

The first human trial examined the pharmacokinetics and safety of fospropofol disodium in 9 healthy volunteers administered doses of 290, 580 and 1160 mg of a 2% solution of fospropofol disodium in 0.4% saline as a 10-min controlled i.v. infusion. The half-life for hydrolysis was 7.2 min. The plasma profile of the prodrug was best described by a 2-compartment model, whereas that of released propofol was best described by a 3-compartment model. Pharmacokinetics were approximately proportional to dose, with mean C_{max} values for the prodrug and propofol of 34.3, 71.6 and 133 μg/ml and 0.77, 1.87 and 3.08 μg/ml, respectively, and mean AUC values of 651, 1113 and 2334 μg/ml.min and 38, 89 and 182 μg/ml.min, respectively; t_{max} was 10.0-11.3 min for the prodrug and 12.0-16.7 min for propofol. Elimination half-lives for fospropofol disodium and propofol were 46 and 477 min, respectively. It was estimated that following a bolus dose of 1000 mg of fospropofol disodium, peak propofol plasma levels of 3.3 ± 0.6 μg/ml would be reached at 7.4 ± 1.2 min (13).

Pharmacokinetic analysis was also performed in 9 healthy male volunteers administered propofol emulsion (10 mg/ml) and at least 14 days later fospropofol disodium (20 mg/ml) as 60-min target-controlled infusions. Results showed that the elimination half-life was shorter for released propofol than for commercial propofol (543 min *versus* 651 min), the central volume of distribution was larger (0.55 l/kg *versus* 0.23 l/kg) and the clearance was also greater (38 ml/kg/min *versus* 24 ml/kg/min). The plasma concentrations of released propofol were similar at both loss and regain of consciousness, suggesting that there is no hysteresis between plasma concentrations and effect, whereas hysteresis was observed for commercial propofol (14, 15).

A phase I crossover study randomized 36 healthy volunteers to receive fospropofol disodium 5, 10, 15, 20, 25 or 30 mg/kg (administered by a 10-s i.v. bolus injection), followed 1 week later by an equipotent dose (as measured by bispectral index) of propofol in its commercial formulation (administered by infusion pump at 50 mg/min). Comparing the disposition of released and commercial propofol, C_{max} was lower (0.6-8.2 μg/ml) for released propofol from fospropofol disodium compared to commercial propofol (7.2-16.3 μg/kg); t_{max} was 3-7.2 min (*vs.* 1.2-4.2 min for commercial propofol). Also, the volume of distribution was larger for released (16.0-24.6 l/kg) compared to commercial propofol (7.9-14.2 l/kg) and the clearance of released propofol was greater (2.8-5.9 l/h/kg) compared to commercial propofol (1.8-2.4 l/h/kg). The time to reach C_{max} was greater at lower than at higher plasma concentrations of released propofol. Overall, the pharmacokinetics of fospropofol disodium and released propofol were best described by a nonlinear 6-compartment model comprised of two 3-compartment models connected by hydrolysis of the prodrug to the active compound (16).

Clinical Studies

In the first human study (13; see above), subjects showed a dose-dependent loss of consciousness (LOC; 0 of 3 on 290 mg, 1 of 3 on 580 mg and 3 of 3 on 1160 mg), with an estimated EC_{50} of 2 μg/ml of released propofol. The drug was well tolerated, with no pain on injection and no apnea; 2 subjects reported transient unpleasant burning or tingling sensation at the start of injection (13). In the other study in healthy volunteers in which propofol released from fospropofol disodium was compared with commercial propofol in the same patients, all subjects showed LOC, with an estimated EC_{50} of 2 μg/ml of released propofol, which was more potent than commercial propofol in the same patients (EC_{50} = 3 μg/ml). The time to LOC was 9 min after initiation of dosing, fractionally more rapid than for commercial propofol at 13 min, and the time to recovery was longer for released propofol (73 min *versus* 47 min following initiation of dosing). Unlike commercial propofol, fospropofol disodium was not associated with pain at the injection site, although all subjects reported sensations of burning, heat or tingling in the genitoanal region (14, 15).

In another target-controlled infusion study, a median MOAA/S (Modified Observer's Assessment of Alertness

and Sedation Scale) score of 4 was achieved in all 12 healthy volunteers with a target plasma concentration of 1.8 μg/ml of released propofol following 1-h infusion of the prodrug (3 subjects had the desired score of 3, 7 had a score of 4 and 2 had a score of 5). Dose adjustments were made in the second hour and a median MOAA/S score of 3 was achieved. The subjects recovered in an average of 18 min after stopping infusion. The propofol concentration with the highest probability of achieving a MOAA/S score of 3 (moderate sedation) was estimated to be 1.9 μg/ml. The majority of subjects had mild to moderate paresthesias or a burning sensation in the lower and upper body or perianal region. A significant decrease in systolic blood pressure and a slight increase in heart rate were reported (17, 18).

The pharmacodynamics and safety were also assessed in the phase I crossover study in 6 healthy volunteers. Confirming the earlier studies, both released and commercial propofol produced a loss of consciousness (MOAA/S < 3) in a rapid and dose-related manner. At fospropofol disodium doses of 20-30 mg/kg and commercial propofol doses of 2.37-5.10 mg/kg, all subjects lost consciousness, with a similar time to LOC. However, the duration of LOC was longer on fospropofol disodium. The peak decrease in bispectral index was also similar on both drugs, although it was reached later on fospropofol disodium. No serious adverse events were reported. Unlike propofol, the prodrug was not associated with pain on injection, although transient paresthesias and pruritus were reported on fospropofol. Fospropofol disodium also showed a tendency for less and shorter lasting apnea (19). Similar results were obtained in another open-label phase I trial in 24 subjects (20).

In a phase II adaptive dose-ranging study, colonoscopy patients received a premedication i.v. bolus of fentanyl citrate 5 min before receiving an initial bolus of fospropofol disodium and up to 4 supplemental doses of fospropofol disodium, with the aim of achieving a MOAA/S score of between 2 and 4. Lean body weight was the best predictor of the dose required to achieve sedation. Neither fentanyl nor gender influenced the pharmacokinetic or pharmacodynamic parameters, but patients over 65 years of age had a 25% stronger effect of the drug at the same propofol concentrations, indicating the need for dose reduction (21-25).

Results were announced from a multicenter, double-blind, dose-ranging phase II study of fospropofol disodium in 127 patients undergoing colonoscopy. Patients were randomized to receive initial bolus doses of fospropofol disodium (2, 5, 6.5 or 8 mg/kg) or midazolam (0.02 mg/kg) following pretreatment with fentanyl citrate. The study design allowed supplemental doses as needed to maintain mild to moderate sedation. The primary endpoint of sedation success (defined as three consecutive MOAA/S scores of 4 or less after the initial bolus, and completion of the colonoscopy without recourse to alternative sedatives or without manual or mechanical ventilation) was statistically superior for the 6.5 and 8 mg/kg groups (75% and 95% success rates, respectively) compared to the 2 and 5 mg/kg groups (24% and 36% success rates, respectively). The midazolam treatment group achieved an 81% success rate. Ninety percent of patients who received fospropofol disodium required 2 or less supplemental doses to achieve initial sedation, compared to 58% of those who received midazolam. According to several secondary endpoints of success, the initial dose of 6.5 mg/kg of fospropofol disodium was superior: adequate sedation during the procedure was reported by 100%, 83% and 89%, respectively, of patients on fospropofol disodium 6.5 and 8 mg/kg and midazolam, overall patient satisfaction was 92%, 79% and 69%, respectively, and investigator satisfaction was 92%, 83% and 77%, respectively. No serious adverse events were reported, and the most common were a temporary burning sensation and paresthesias (26-28).

MGI Pharma has initiated two multicenter, randomized, double-blind phase III trials of fospropofol disodium in patients undergoing colonoscopy and bronchoscopy (29-31). A phase II/III clinical trial evaluating the safety of fospropfol disodium for sedation during minor surgical procedures following pretreatment with fentanyl (32) is also under way.

Source

MGI Pharma, Inc. (US).

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