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ATC code:
N03AG01

Classification:
P - Porphyrinogenic

Substance:
Valproic acid

Rationale for risk classification:
There are several reports in the literature of valproic acid precipitating acute porphyric attacks. Two reports are well documented and the causality is probable. Induction of CYP 3A4 and CYP 2B6, and mechanism based inhibition of CYP 2A6 has been shown in vitro, but the potency and clinical significance is not well documented. Valproic acid has been associated with increased activity of ALAS, the rate-limiting enzyme of the heme biosynthesis, and may therefore be porphyrinogenic.

Chemical description:
Carboxylic acid

Therapeutic characteristics:
Valproic acid is an anticonvulsant thought to potentiate the inhibitory action of gamma amino butyric acid (GABA). It is used in the treatment of generalized, partial and other epilepsy seizures and in the treatment of bipolar disorders. It is administered orally or as an injection. It has an elimination half-life of 8-20 hours.

Metabolism and pharmacokinetics:
Valproic acid is metabolized by glucuronide conjugation (50 %), beta-oxidation (40 %), and oxidation (10 %) by different CYP enzymes (CYP2C9, CYP2C19, and CYP2A6) (Flemming 2005).
Valproic acid is found to be an inducer of CYP 3A4 in an in vitro study and the authors suggest that it may interact with other CYP 3A4 substrates at clinically relevant plasma concentrations (500 to 1000 microM) (Cervency 2007). Clinical reports of CYP 3A4 interactions with valproic acid seems to be lacking and interaction search databases does not list valproic acid as a drug with CYP interaction potential. Valproic acid does not alter the pharmacokinetics of CYP 3A4 metabolized oral contraceptive steroids (Crawford 1986).
In another in vitro study valproic acid is found to be a competitive inhibitor of CYP 2C9 and CYP3A4 (weak)
and a mechanism based inhibitor of CYP2A6 (weak) (Wen 2001).

Valproic acid is also found to be an inducer of CYP2B6 in vitro (Takizawa 2010).

In an in vivo study, valproic acid was found to increase the activity of leucocyte ALAS in normal individuals, which also resulted in increased urinary excretion of porphyrins and their precursors (McGuire 1988). The mechanism behind this ALA stimulation is unknown.

**Published clinical experience:**

Well described case reports of valproic acid as a precipitant of porphyric attacks are published by Doss et al (1981) and Garcia-Merino et al (1980). Several other reports also describe porphyric attacks in patients where valproic acid is suspected as a triggering agent (Herrick 1989, Suzuki 1992).

**EPNET drug reports:**

Uneventful use reported in 3 patients with acute porphyria.

**References:**


