

Naftidrofuryl oxalate induced hepatitis

Naftidrofuryl oxalate induced hepatitis is uncommon but is a serious and potentially fatal complication. There is some evidence of clinical efficacy of naftidrofuryl oxalate in peripheral vascular disease and in May 2011 it was recommended by NICE. Naftidrofuryl oxalate is therefore likely to be used more frequently and so the incidence of hepatitis associated with it could increase. It is important to include drug induced hepatitis in the differential diagnosis in patients presenting with abnormal liver function tests.

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Abnormal liver function secondary to medications is not uncommon especially in older people with multiple comorbidities and polypharmacy. It is estimated that approximately 10% of acute hepatitis related hospital admissions are due to medications. There is a varying degree of drug induced liver toxicity from mild elevation of transaminases to acute hepatic failure.

Clinical evidence

Peripheral vascular disease (PVD) affects around 12–14% of the general population and about 20% in those over 70 years.¹ Naftidrofuryl oxalate is used in the treatment of PVD as an

oral peripheral vasodilator that selectively blocks vascular and platelet 5-hydroxytryptamine 2 (5-HT₂) receptors causing a vasodilator effect. However, the clinical evidence for efficacy of naftidrofuryl versus placebo in individual clinical trials is unclear. None of the trials that measured Ankle Brachial Pressure Index showed any improvement after three to six months of treatment. (Table 1)^{1–8} In a meta-analysis, four trials have demonstrated a modest increase in patient's pain free walking distance (PFWD).⁹ Two trials did not show any improvement in the mean walking distance (MWD). The duration of the trials were typically three to six months and thus there are no long term efficacy data. Based on the weak

evidence the drug has not been approved by the US Food and Drug Administration (US FDA). However, in May 2011 NICE approved naftidrofuryl oxalate as an option for the treatment of intermittent claudication in people with PVD. Although naftidrofuryl oxalate does not stop the progression of PVD it was felt that it could be useful in increasing walking distances in patients with PVD.¹⁰

Adverse effects

The main adverse effects of naftidrofuryl oxalate are gastrointestinal, which include nausea, epigastric pain, diarrhoea and hepatitis. None of the trials highlighted hepatitis or hepatic failure possibly due to

Box 1: Efficacy evidence from clinical trials

Study/year and duration*	Population*	Age range	Outcome	Benefit
Adhoute et al, 1986. 6M	64/54	40–70	PFWD ABI	PFWD difference 103m (p<0.02) ABI no statistical difference
Adhoute et al, 1990. 6M	52/42	40–70	PFWD MWD ABI	PFWD (180d) 123m (p<0.05) MWD 177m ABI no statistical difference
Boccalon et al, 2001. 12M	67/55	40–80	PFWD MWD	PFWD 107% naf vs 12% control (p<0.001) MWD 74% naf vs 1%
Keiffer at al, 2001. 8M	98/98	35–85	PFWD MWD ABI	PFWD 91.8% naf vs 16.8% control (p<0.001) MWD 82% naf vs 13.9% ABI no statistical difference
Kriessman et al, 1988. 3M	71/65	40–70	PFWD MWD ABI	PFWD 91.8m naf vs 42.3m control (p<0.05) ABI no data
Maass et al, 1984. 3M	54/50	40–70	PFWD MWD ABI	PFWD difference 59m (p<0.05) MWD No statistical difference ABI no data
Moody et al, 1994. 6M	85/95	40–80	PFWD MWD ABI	PFWD no statistical difference MWD no statistical difference ABI no statistical difference

*Months, **population: refers to the number of patients who made it to randomisation for naftidrofuryl versus the control group, PFWD = Pain Free Walking Distance, MWD = Mean Walking Distance, ABI = Ankle Brachial Index.

the short duration of the trials and small number of population included. Few cases reported naftidrofuryl oxalate induced hepatic damage.¹¹⁻¹³ Hepatitis associated with naftidrofuryl oxalate is uncommon but it is a serious and potentially fatal complication. The liver damage is usually extensive and transaminases usually rise by 50 times the normal upper limit. De Caestecker and Heading¹¹ describe a 60 year old woman who was believed to have developed acute hepatic necrosis secondary to naftidrofuryl oxalate. The patient's liver function test showed a bilirubin of 545µmol/L (normal 2-17) and an ALT of 1854 units/L (normal 10-40). A liver biopsy was performed and this revealed extensive centrolobular necrosis and inflammatory cell infiltrate.

Conclusion

The evidence for naftidrofuryl efficacy is at best modest and long term efficacy is unclear. Although hepatitis associated with naftidrofuryl oxalate may be infrequently reported in the literature at present, the incidence of it is likely to increase after the recent NICE guidance. It is important that naftidrofuryl oxalate induced hepatitis is recognised and considered in the differential diagnosis in patients who are on the medication.

It has been reportedly misdiagnosed and has led to unnecessary cholecystectomy.⁴ It is important that once recognised, the drug is discontinued early. If the medication is withdrawn

early there is likely to be complete recovery of liver function.

Conflict of interest: none declared

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