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THE CONCENTRATION OF THUJONE IN ABSINTHE FROM VALENTIN MAGNAN'S TIME

The recent paper on absinthe, epileptic seizures and Valentin Magnan (Eadie MJ. Absinthe, epileptic seizures and Valentin Magnan. *J R Coll Physicians Edinb* 2009; 39:73–8) addresses an interesting question: can science from the 1870s be of any validity for today's view on the alcoholic beverage absinthe?

In an attempt to defend Magnan's conclusions on the responsibility of absinthe to cause epileptic seizures in humans, Eadie argues that the presence of thujone at convulsant concentrations in some of the available absinthes of Magnan's time cannot be known. We have demonstrated, however, that it can be known: not only from theoretical calculations,[1] but also from chemical analyses of surviving products.[2,3] The total thujone content in 21 analysed pre-ban absinthe samples ranged between 0.5 and 48.3 mg/l, whereas the average thujone content of 27.8 ± 17.1 mg/l fell within the modern Codex Alimentarius/EU limit of 35 mg/l (derived from no-effect levels in animal experiments with an additional safety factor). We also provided evidence that thujone in bottled absinthe remains stable; therefore, our analyses of 100-year-old spirits were not confounded by significant thujone deterioration over time.[3] We concluded that the scientific literature contains no proof that historic absinthe contained thujone in concentrations able to produce any of the effects experienced in the Magnan experiments conducted with pure wormwood oil. Our historical survey[4] also showed that Magnan was swayed by specific anecdotal reports from which he inferred a general principle. Magnan attributed the epileptic seizures and general delirium observed in long-term absinthe drinkers to wormwood essence in absinthe in particular, rather than to alcohol in general, which is the more plausible explanation.

Another of Eadie's claims, which seems highly speculative, is that some of Magnan's patients might have had a genetic predisposition to juvenile myoclonic epilepsy (not described at the time) and thus may have been unusually vulnerable to thujone's convulsant effect. The relationship Magnan drew between absinthe and epilepsy was not restricted to a small number of drinkers, but to all of them.

In conclusion, we want to stress that while Magnan's conclusion on absinthe cannot uphold to today's standards, he is still rightly regarded as one of the fathers of French psychiatry.

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3 Lachenmeier DW, Nathan-Maister D, Breaux TA et al. Long-term stability of thujone, fenchone, and pinocamphone in vintage preban absinthe. *J Agric Food Chem* 2009; 57:2782–5.
4 Luauté JP. [L'absinthisme: la faute du docteur Magnan]. *Evol Psychiatr* 2007; 72:515–30. In French.

Author's reply

The various publications that Drs Luauté and Lachenmeier have cited in their letter provide persuasive evidence that specimens of some absinthes that have survived intact from as long ago as 1895 did originally contain concentrations of the convulsant thujone that would be considered acceptably safe today. However, as far as I can make out, the publications do not seem to provide data for the thujone concentrations that were present in the absinthes that Magnan's patients actually imbibed at an earlier time, in the decade centred on 1870, the period when his investigational work was done. Such absinthes may have differed from later ones in thujone content, and involved sources which have long ceased to exist. As yet, there seems no way of being sure.

Moreover, thujone concentration in absinthe is unlikely to be the sole determinant of any tendency to epileptic seizures associated with absinthe exposure. There is also the issue of the inherent epileptogenicity of the sufferers' brains, hence the suggestion that a predisposition to juvenile myoclonic epilepsy may have been expected to increase any risk of thujone-associated seizures. A second issue, probably, is the thujone concentration present at the cerebral sites of seizure genesis. Among other factors, this concentration would probably depend not only on the thujone concentration in the absinthe ingested, but on the volume of absinthe swallowed and the period of time involved in the intake. No information appears to be available concerning the latter two matters in Magnan's subjects.

Certainly, the high quality analytical chemical work of Dr Lachenmeier and his colleagues does not support Magnan's interpretations of the relation between absinthe intake and epileptic seizures. However, by itself, it also does not seem sufficient to refute his conclusions. So many years after the event, it seems unlikely that evidence adequate to fully resolve the issue will ever become available.

Prof. MJ Eadie

OVERDRINKING AND HYPONATRAEMIA

It is a great pity that in their excellent article on hyponatraemia Thompson and Crowley (Thompson CJ, Crowley RK. Hyponatraemia. *J R Coll Phys Edinb* 2009; 39:154–7) made no mention of hyponatraemia induced by overdrinking. This is now a widely recognised hazard for

athletes, especially distance runners, and has been the cause of many deaths in very fit and healthy young people.[1] This is due to the 'liquid refreshment' industry trying to translate good laboratory research into the different situation in the field.[2] Unfortunately the drinks industry is now so profitable and powerful that they are still pushing people to drink a lot of fluid. This financially driven momentum has now led to hyponatraemia occuring in patients during labour, increasing the hazards of birth.[3] It is time this drive to keep everybody drinking at all times is stopped.

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3 Moen V, Brudin L, Rundgren M et al. Hyponatremia complicating labour – rare or unrecognised? A prospective study. *BJOG* 2009; 116:564–73.

The original authors were shown the above letter but declined to comment on the points raised.

SINGLE- VS DOUBLE-CHAMBER PACEMAKERS

We read with interest the article by Choo WK et al. in the June edition of the *Journal* (WK Choo, L Tilling, S Gupta. The selection of pacing modalities according to NICE recommendations. *J R Coll Physicians Edinb* 2009; 39:113–6). In their study they correctly state NICE guidelines currently recommend dual-chamber pacemakers for those with high-degree atrioventricular (AV) block, and their current practice reflects this. It is noteworthy that the UKPACE investigators randomised 2,021 patients over the age of 70 years with second- or third-degree AV block to a single-chamber pacemaker (n = 1,009) or dual-chamber pacemaker (n = 1,012) and followed them up for a median of 4.6 years.[1] They found no significant clinical benefit from dual-chamber pacemaker, but in fact an increased risk of complications in the dual-chamber group. The authors conclude that in subjects older than 70 years of age with high degree AV block, single-chamber pacemakers are warranted.

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Reference

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The original authors were shown the above letter and valued the points raised.

ALLOPURINOL AND STEVENS-JOHNSON RISK

Dr Foong helpfully highlights the well-established rare link between allopurinol and Stevens-Johnson syndrome, by reviewing the results of the EuroSCAR study (HBB Foong. Allopurinol and the risk of Stevens-Johnson syndrome and toxic epidermal necrolysis. *J R Coll Physicians Edinb* 2009; 39:144–5). At rates of two per million population, it remains an extremely unusual phenomenon. His conclusions that 'more often than not the drug is prescribed for asymptomatic hyperuricaemia' are erroneous and lack evidence. The retrospective report of eight patients from 23 years ago and literature review which he quotes clearly do not provide a clear enough sample size to form a judgement.

Hypersensitivity of a more benign nature is frequently mentioned as a reason for discontinuing allopurinol. However, it is estimated that 95% of patients are able to tolerate allopurinol.[1] Side effects can include rash, diarrhoea, leukopenia, pruritis and fever. If the manifestations are only cutaneous, then desensitisation can be attempted commencing at doses as low as 50 µg and increasing to 100 mg over a four-week period. More than 70% of such patients are able to continue to take allopurinol, although sometimes late adjustment of the dose may be required. Education for practitioners regarding desensitisation regimens should allow more patients to tolerate the drug. Gout is undertreated at present, and patients should be on doses of allopurinol that allow a serum urate of <0.36 mmol/l.[2,3] Dose titration can escalate to 900 mg if required. Undertreatment leads to flare and tophaceous disease, with radiographic damage and disability.[4]

Adverse reactions with allopurinol are unfortunate but extremely rare and should not be used as a reason for lowering the appropriate dosage of allopurinol as agreed in both national and international guidelines.[2,3]

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4 Dalbeth N, Collis J, Gregory K et al. Tophaceous joint disease strongly predicts hand function in patients with gout. *Rheumatology (Oxford)* 2007; 46:1804–7.

Author's reply

I thank Dr Perry for his interest in my article. I agree with him that if the manifestations of the side effects of

allopurinol are mild, then desensitisation can be attempted at a lower dose. However, isolated asymptomatic hyperuricaemia does not warrant the use of allopurinol. One must distinguish the difference between gout and hyperuricaemia. Dr Perry's references on the rheumatology guidelines for the management of gout apply to cases of gout and not to hyperuricaemia.[1] In fact, the indications for allopurinol therapy are tophaceous gout, major uric acid overproduction (proven by urinary excretion >53 mmol/24 hours) frequent gouty attacks, recurrent uric acid renal calculi and prevention of acute urate nephropathy in patient receiving cytotoxic therapy for malignancies.[2]

In a study by Khoo[3] a total of 13 patients were admitted for severe cutaneous adverse reactions to allopurinol during a three-year period. Almost 92% of them suffered from allopurinol hypersensitivity reactions, which included four patients with Stevens-Johnson syndrome. Allopurinol hypersensitivity syndrome, in contrast to other purely cutaneous drug eruptions, deserves special attention because of its multi-organ involvement, the liver and kidneys being most commonly affected. It was interesting to note that none of the 13 patients had clear clinical indications for allopurinol therapy. Asymptomatic hyperuricaemia is not uncommon, affecting an estimate of 5–8% of the population. As the risks, morbidity and mortality outweigh the benefits, it should only be prescribed when it is truly indicated.

Dr HBB Foong

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HEPARIN-INDUCED THROMBOCYTOPENIA AND THROMBOSIS

I read with interest the article 'The diagnosis and treatment of acute pulmonary thromboembolism' (TN Martin, AJB Brady. *J R Coll Physicians Edinb* 2009; 39: 107–12) and would like to give some comments.

Firstly, the authors did not mention important hereditary and acquired thrombophilic conditions such as anti-phospholipid antibody syndrome, factor V Leiden and pro-thrombin gene mutations, protein C, protein S, antithrombin III deficiencies as risk factors for venous thromboembolism. In my opinion, they are worth mentioning.

Secondly, with increasing prophylactic and therapeutic use of heparin, I would like to point out that development of heparin-induced thrombocytopenia (HIT) and thrombosis (HITT) is not rare. The incidence for HIT ranges from 0.1% to 5% depending on the type of heparin used and the risk group of patients. Approximately 40% of patients with HIT subsequently develop thrombosis. Of note, 26% of patients are noted to have concurrent thrombocytopenia and thrombosis.[1]

The condition is usually typical in that thrombocytopenia (either below 150,000/mm^3 or 50% decline in baseline platelet count) develops within 5–10 days of heparin use in patients who have had no heparin exposure or who have had remote history of exposure (more than 100 days). Rarely, precipitous fall in platelet count can occur within hours if there is recent exposure to heparin.[1]

The management of acute pulmonary embolism due to HITT is entirely different. In those patients, heparin must be avoided. Anticoagulation is commenced with direct thrombin inhibitors such as lepirudin or argatroban. Warfarin therapy should be postponed until there has been substantial resolution of thrombocytopenia as warfarin therapy is associated with a severe reduction in the natural anticoagulant protein C, making the hyper-coaguable state worse during the acute phase of HITT.[2]

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Authors' reply

We welcome Dr Oo's comments on our review. His suggestion to check for genetic and acquired abnormalities of coagulation, for example factor V Leiden mutation and others, is worthwhile, particularly if there is no obvious precipitating factor causing the venous thrombosis. Of course, initial management is unaffected by these investigations, the results of which would not be available until long after the acute phase of therapy. This is addressed in the pre-penultimate paragraph of our review, together with a list of special situations that includes heparin-induced thrombocytopenia, which directs the reader to the full discussion in the European Society of Cardiology guideline.[1] The overriding aim of our review is to highlight the crucial importance of immediate determination of risk of death from pulmonary thromboembolism, with appropriately directed treatment.

Dr Thomas N Martin, Dr Adrian JB Brady

Reference

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