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Meta description (<300 char/~50 words)	An analysis placing in perspective the relative risk of typical elevations of blood pressure caused by excessive tyramine in the diet, and other drugs, compared with common activities such as sports which produce similar elevations of BP.

The risk of harm from acute tyramine-induced hypertension: how significant?

Abstract

There has been a long-standing presumption, ever since the original problems in the 1960s, that MAOIs produce a special risk of subarachnoid haemorrhage (SAH). That was why MAOIs were briefly removed from the market (at least in the USA, but not the UK) until a greater understanding of tyramine, and the role of cheese, was gained, and Tyr restricted diets were recommended. However, a more sophisticated understanding of this problem never emerged because MAOIs fell out of use quickly and there was little research interest in the clinical aspects of their use and side effects. An updated informed understanding of this reaction, and of the much lower levels of Tyr in modern-day foods, leads to a useful reassessment of the risk.

Extensive evidence now indicates that the degree of transient Tyr-induced elevation of blood pressure is typically no greater than that associated with many common activities, including sports and other regular life activities.

Furthermore, the relationship between transient episodes of acute hypertension and the occurrence of SAH is now understood not to be a simple cause-effect relationship. The possibility of Tyr-induced hypertension being associated with subsequent SAH would appear to have been both over-emphasized and over-estimated.

Introduction and perspective

MAOIs **lower** BP: one of the more common incorrect statements you will see is that MAOIs raise BP. In the 1960s MAOIs were used to treat hypertension (1-4); they worked, but better drugs were soon found.

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Deaths from tyramine/MAOI induced acute transient hypertension causing **subarachnoid haemorrhage (SAH)** are rare, probably as rare as serious and fatal reactions to various more commonly used drugs for example: allergic reactions to penicillins; toxic epidermal necrolysis (caused by anticonvulsants like lamotrigine, and sulphonamides, antifungals, allopurinol, and NSAIDs); liver failure from valproic acid; or neuroleptic malignant syndrome (NMS) from anti-psychotics.

Of all drug related deaths, the commonest is GI bleeding from NSAIDs, accounting for 12,000 ulcer bleeding episodes and 1200 deaths **per annum** in the United Kingdom (5-7): approximately 2/100,000 per year. It has been suspected for many years that GI bleeding is exacerbated by SSRIs (8-11). GI bleeds still have a 10% mortality, and those on SSRIs may be twice as likely to die (12, 13). Doctors do not worry, or exhibit such risk aversion, in relation to these problems, compared to MAOIs: there are several cognitive biases at work here, summed up by the old sayings; 'familiarity breeds contempt'; and 'what the eye does not see, the heart does not grieve over'.

A reminder of the relative risks of these other drugs, that generally receive much less attention and concern, is appropriate in order to achieve a sense of proportion. How many doctors who prescribe SSRIs enquire into the patient's history of dyspepsia, gastritis, or GI haemorrhage? I estimate such prescribing exposes such patients to a similar or greater degree of risk, compared to giving MAOIs.

The likelihood of elevated BP due to **tyramine (Tyr)** ingestion is substantially less now than in the past, because the amount of Tyr in modern foods is significantly lower (14) and therefore the degree of elevation of BP, and its duration, will both be of a lesser degree — **the pressor response is a dose related effect and is transient** (1-2 hours). It is now exceptional for normal portions of modern foods to contain sufficient Tyr (20-50 mg) to precipitate a *potentially* serious reaction (the FDA has designated 40 mg of Tyr as a 'Tyr-rich' meal). Although I agree with that, I am unsure how they come to that estimation, since the source has no references. My recent review of current evidence demonstrates that nowadays it is rare for any cheese to contain as much as 300 mg/kg per of Tyr (14): this means that even a portion of 100 g (three-times the recommended portion size) contains only 30 mg.

Contributory factors associated with subarachnoid haemorrhage (SAH)

The most significant enduring factors associated with **subarachnoid haemorrhage (SAH)** are pre-existing aneurysm or arterio-venous malformation (85% of clinical presentations (15)), hypertension, smoking, and diabetes; and acutely, cerebral trauma. Despite the enormous numbers of people who take excessive quantities of illicit drugs that raise BP, such as amphetamines and other releasers **(indirectly acting sympathomimetic amines, ISAs**), and cocaine, these are rarely reported as contributors to episodes of SAH (16). Over the years there have been occasional reports of SAH associated with most drugs that elevate BP, including caffeine, ephedrine and the alpha agonists such as midodrine (17-22); and also with many physical activities and sports, which elevate BP to a greater or lesser degree — but again, rarely.

There are rare reports of SAH associated with most BP-elevating drugs, e.g., caffeine, ephedrine, amfetamine, midodrine

Reports of SAH associated with such drugs and physical activities are clearly a rare association, indicating that acutely elevated BP is not a 'causal' factor, but one 'triggering' or precipitating factor, among others. An analogy is that of the

seaworthiness a boat: any boat can be overwhelmed by a rogue wave, but a boat that is overloaded will founder, even in an 'ordinary' weather. However, to blame one particular wave for its sinking does not make sense. Similarly, for those who are constitutionally susceptible to SAH, it is probably going to occur sooner or later, either for non-specific reasons, as the chronic factors mentioned above exert their influence, or in response to a short-term increase in BP caused by any one of the 'normal' and inevitable regular increases in BP associated with living and usual activities.

Normal blood pressure variation

There are many common activities that frequently raise the BP **in excess of 200-300 mmHg** for relatively short periods of time (minutes, or an hour or two). Healthy vigorous exercise will increase systolic BP to **at least 200** (see below), where it will remain throughout the duration of the exercise: remember the popularity of marathon running and triathlons.

A recent paper reported on exercise measurements in nearly **2,000 Olympic athletes**, and even these super-fit persons had high BPs (23). A total of 1,876 healthy, normotensive elite athletes (aged 25 ± 6 years, 64% male) underwent a comprehensive clinical evaluation including maximal bicycle exercise test. **About 10% had SBP of 220-250**: the authors concluded; 'the reference values for maximal systolic BP (calculated as 95th percentile) are 220mmHg in male, and 200mmHg in female athletes'.

> The typical maximal systolic BP in athletes is 220mmHg

I have a medical colleague who used to play rugby for the New Zealand 'All Blacks'. He regularly ran the 8 km to the clinic where he worked which was atop of a 70m high hill (sometimes wearing an 8 kg lead diving-belt); he went flat out up the final hill, and he measured his BP when he got there. It was usually 300. He remains fit and healthy aged 70: his recent exercise test with his cardiologist gave an exercise reading (which he would gauge at ~80% effort) of 248/100.

One of his contemporaries, the renowned Welsh player Mervyn Davies (aka 'Merve-the-swerve'), suffered SAH while playing in a match.

https://en.wikipedia.org/wiki/Mervyn_Davies

More data

Pressler et al. reported on cycle ergometry **performed in 2,400 competitive athletes** (24). They concluded the increase in SBP induced by dynamic exercise testing exceeded common limits in a considerable proportion of athletes. The estimated **upper normative limit of mSBP (97.5 centile) was 247mmHg in men and 214mmHg in women**.

> Many athletes undergoing cycle-ergometry-testing develop BPs of 250 mm Hg

Less fit amateur sportsmen may develop even higher pressures during their activities.

The Mayo clinic published results of screening of the peak exercise BP in **10,000 apparently healthy subjects** and they found the 90th percentile of SBP increased **from 210 for 20-29 year-olds to 234 for 70-79 year-olds** (females 180-220) (25) — that test procedure would not be as prolonged or strenuous as the athletics maximum-exertion test.

Gym exercises with weights, and weightlifting, elevate BP in excess of 300, and sometimes as high as 450 mmHg. Large numbers of amateurs and professionals engage in this activity: there are but a handful of reports of SAH (26-31).

Activity and risk

As Anderson's work suggests (32), exercise may marginally increase the incidence of SAH in the immediate short-term, although in the long term it protects against stroke. It may be noted that neurosurgeons do not usually advise people to avoid strenuous exercise after they had suffered SAH.

> Neurosurgeons do not advise avoidance of strenuous exercise post SAH surgery

A recent large series of prospectively collected SAH cases from one center by Nanji (16) contains data relating to sporting activity. **Out of the 738 cases**, SAH onset occurred at rest in 157 (21.3%), a small proportion (9 cases) were associated with the practice of a sport (1.2%), illicit drugs do not even get a mention. SAH occurred after various activities: running (2 cases), aerobics (2 cases), cycling, body balance, dance, surf and windsurfing. All bar 1 patient had vascular risk factors, and 1 a history of cocaine use.

The doctor in charge of the London Marathon (tens of thousands of participants) has stated that there was only one death from SAH in 20 years (33); i.e. ~1/500,000).

BP is clearly substantially elevated during sexual intercourse (34), and as I said in a previous comment, a typical Tyr pressor response is probably not 'any greater than those (hopefully) experienced when engaging in vigorously amorous pursuits with our partners, or weightlifting, or a combination of the two' (34, 35). A case series relating to SAH and sexual intercourse has been reported (36) — many tabloid newspaper stories exist describing men who have died whilst visiting their mistresses (remember Downton Abbey).

Summary and conclusion

All sporting activities and activities that involve exertion have, however rarely, been associated with the onset of SAH. Likewise, the ingestion of various drugs that have greater and lesser effects on BP have also been so-associated. It is established from extensive reliable data that SAH associated with transiently elevated BP is rare and the vast majority of subjects engaging in the many common activities that increase BP into the 200-250+ range do not suffer from SAH.

The elevations of BP encountered in clinical practice, and in case reports, of Tyr-induced hypertension are of the same magnitude and duration as those discussed above — indeed, that may reflect the fact that Tyr is triggering release of adrenaline from adrenal medullary cells, in essentially the same way as the 'fight and flight' mechanism with which nature has equipped us: one might presume that selection pressures of evolution would not have enabled the successful survival and reproduction of those individuals whose blood vessels burst every time they became aroused squabbling over a female, or every time a lion leapt out from the jungle to chase **them***.

These data make it reasonable to conclude that the vast majority of elevations of BP due to the ingestion of Tyr whilst on MAOIs are unlikely to constitute a greater risk for the precipitation of SAH than many other 'normal' activities — this conclusion may be considered reliable, especially because Tyr levels are much

* I occasionally insert deliberate mistakes —Tigers live in the jungle, not Lions. One astute reader has emailed me, having noticed this mistake.

lower in modern foods compared to the high levels of 3,000 mg per kilogram that were assayed in some of the early reports by Blackwell and others (37, 38) — most modern cheeses have less than 300 mg per kilogram: one 10th as much.

These data strongly suggest that occasional accidental ingestions of slightly excessive amounts of Tyr, that may occur whilst patients are taking MAOIs, do not produce a risk of harm of any significant magnitude, and not to a greater extent than many other normal activities.

It may also be noted that neurosurgeons do not advise people with known malformations, or previous SAH, to avoid sports etc. This raises the question of whether it is necessary to regard a known pre-existing malformation as an absolute contraindication to MAOI treatment (as has traditionally been opined). In most cases this will be a theoretical consideration, since such malformations are not usually known about until after the event.

The level of concern that has been common among psychiatrists for a long time would appear to be without substantive foundation. Paradoxically, it may have given rise to a greater degree of iatrogenic harm as a result of hasty and unwarranted intervention with BP lowering drugs: there are a number of instances of hypotensive ischaemic stroke as a result of treatments, like sublingual nifedipine (39-49), the use of which is strongly advised against, especially if given to patients to take as a 'rescue medication'. Such treatments are probably helping the anxiety of the treating doctor, rather than treating the body of the patient — indeed they probably cause a greater risk of harm by lowering BP too quickly in insufficiently supervised environments (such treatments are only advised when there is clear evidence of end organ damage, and in critical care units).

Extensive evidence indicates that enormous numbers of people experience such degrees of elevated BP (200-250) without harm. Furthermore, if they do have the constitutional susceptibility to SAH, then it is going to happen sooner or later for 101 other reasons: there is no evidence of a *causal* link between infrequent episodes of hypertension and SAH, even the cause-effect nexus between repeated episodes and SAH is tenuous.

If the above argument it is not considered convincing then it would seem the alternatives are to accept that life comes with risks, or to consider banning (if it were possible), among other things, heated arguments, sex, exertional sports, caffeine containing drinks, and a range of other drugs. One might assert that such a course is neither possible, nor sensible, nor logical, nor acceptable. We would die of boredom instead, before experiencing a stroke due to lack of activity.

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