CALCIUM CHANNEL BLOCKERS AND HYPERTENSION

A number of readers have called Bandolier to ask if we would explain the current controversy about the association between calcium channel blockers and myocardial infarction in hypertension. This is a tall order, and one that we probably can’t fill in its entirety. What Bandolier can do, however, is to give a synopsis of the evidence from the two recent publications [1,2] which precipitated the row.

Case-control study [1]

623 hypertensive patients in and around Seattle who were members of a group health cooperative who had a first fatal or non-fatal myocardial infarction were the cases. The 2032 controls were a stratified random sample of hypertensive patients matched for age sex and calendar year.

Excluded were people who had been members of the scheme for less than one year, who did not have a diagnosis of hypertension, who had a prior myocardial infarction or whose infarction was a complication of a procedure or surgery. Patients had to have been taking antihypertensive medicines for at least 30 days because preliminary analysis showed that recent starting of ß-blockers and calcium channel blockers was strongly associated with a risk of myocardial infarction.

Dose-response analysis was conducted by selecting patients taking the modal dose as the middle group, with those with lower or higher doses comprising the other two groups.

Results

A first analysis included only patients who were free of clinical cardiovascular disease (upper graph). There was a powerful association between myocardial infarction and calcium channel dose, alone or in combination with diuretics. The risk at the highest doses of calcium channel blockers was three times that at the lowest doses (upper graph), with an NNT for myocardial infarction of about 35 (19 - 264) for CCB alone and 59 (28 - >500) with diuretics.

For every 35 (or 59) patients treated with high dose CCB, one would have a myocardial infarction over the next five years who would not have if they had not been given this treatment.

Analysis across all patients showed the same relationship, a relationship which was not apparent for other medicines, for example, ß-blockers (lower graph).

These effects of higher rates of myocardial infarction with calcium channel blockers appeared to be consistent with a number of different compounds. For patients taking a calcium channel blocker, compared with those taking a ß-blocker, there was a 60% increased risk of myocardial infarction.
Systematic review of nifedipine [2]

Authors who were involved with the case-control study assessed dose-related increases of mortality in patients with coronary heart disease through a systematic review.

They found 16 randomised controlled studies in which nifedipine was used in doses from 30 mg/day to over 100 mg/day. Twelve of the trials randomised patients with myocardial infarction, three included patients with unstable angina, and one evaluated patients with stable angina, some of whom had a prior infarction. In all there were over 8,000 patients. The outcome measure of the review was mortality.

Results

At doses between 30 and 50 mg/day there was no excess mortality.

Four trials with 2,400 patients used 60 mg/day. The risk ratio was 1.18, and although the confidence intervals included 1, two of the trials were stopped early because of increased mortality or increased reinfarction. This may have led to an underestimate of the adverse mortality effect of the 60 mg/day dose.

Four trials with almost 800 patients used 80 mg/day. The risk ratio was 2.8 (1.4 - 5.9) - a three-fold increased risk.

Comment

These two papers come from the same “stable”. They are thoughtful and apparently well conducted. The discussions need to be read to get a full flavour of this complicated subject. Ongoing large scale trials will provide much more information on the effects of various hypertensive therapies, but in the meantime these papers provide food for thought where calcium channel blockers are prescribed in high doses. US guidelines recommend the use of diuretics and β-blockers as first-line agents unless contraindicated, unacceptable or not tolerated.

References:


Evidence-based eating

Trying to make sense of diet and health has not been helped by the apparently divergent views that have been published over the years. To find some solid evidence with large effects from a reputable source is particularly welcome.

Fruit & veg prevent stroke in men

From the Framingham study, a cohort study of 832 middle aged men has examined the effects of eating fruit and vegetables on the risk of stroke. They were free of cardiac disease at the start of the study, which had a 20-year follow-up.

Design of the study

The diet of each subject was assessed at baseline from a single 24-hour recall. The estimated number of servings of fruits and vegetables was used to differentiate the men into five groups (quintiles) of increasing vegetable intake. The intake of the lowest group was 0-2 servings a day, that of the middle group was 5 servings a day, while that of the group with the highest intake was 8-19 servings a day (mean 10).

A serving was defined, roughly, as 120 mL (half a cup) for fruits and vegetables, 60 mL for tomato sauce, 120 mL for peas, beans and corns, 28g or potato chips (crisps), or a single potato.

During a follow-up period of 18-22 years all cardiovascular events, including stroke, were reviewed by a panel of three
physicians who used a set of established criteria. For stroke outcomes the panel included at least two experienced neurologists. Minimal criteria for stroke included abrupt onset of a localised neurological deficit. Stroke was further characterised into ischaemic, or haemorrhagic stroke. Transient ischaemic attacks (TIA) were recorded separately.

Results

Despite the large differences in diets, there were few differences between the men in the five groups (mean age 56 years at baseline) for systolic blood pressure, serum cholesterol, ethanol intake or physical activity index. Men with the largest fruit and vegetable index tended to have a slightly higher body mass index and they smoked fewer cigarettes and had a higher energy intake.

As the number of servings of fruit and vegetables increased, the number of stroke events decreased. In men eating the lowest amount of fruit and vegetables, 19 of 100 had a stroke compared with only 8 of 100 among men eating the highest amount. Similarly the number of completed strokes fell by nearly two thirds from nearly 15 of 100 to 6 of 100 from low to high fruit and vegetable intake.

What is the mechanism?

There doesn’t seem to be a satisfactory answer to this. The authors looked for all sorts of confounding variables, and their discussion is interesting in itself, but there seems to be a protective effect of fruit and vegetables against stroke.

Take home message

Eating quite moderate amounts of fruit and vegetables can substantially reduce the risk of a stroke.

Reference:


FALLS IN THE ELDERLY

Falls and the injuries they cause are of major medical importance in the elderly. A recent planned meta-analysis of trials of short-term exercise in over 2,000 elderly people in the United states show that exercise can help prevent falls over the next 2-4 years.

The size of the problem

In the United States it has been estimated that 30% of people over 65 years have a fall in any one year, and half of these 30% have more than one fall.

The consequences of a fall in the elderly can be serious. Perhaps one in 10 falls results in serious injuries, with up to 1% of falls resulting in a broken hip and a further 5% resulting in other broken bones. The injuries elderly people sustain result in impaired movement and life quality, and the pain and disability can continue for a median of seven months in 40% of elderly people going to hospital after a fall. Apart from the pain and distress for the individuals, falls in the elderly are sufficiently common to comprise a major part of health care costs.

Setting

Independent randomised controlled trials were carried out in two nursing homes and five community dwelling sites in the USA. Numbers of elderly people included varied from 100 to over 1,300 (minimum ages varied from 60 to 75 years). The studies each included a control group. Those in the treatment groups had 10 to 36 weeks of one of a number of different interventions, including different exercise regimes with resistance and/or endurance training, nutritional instruction, meditation, and Tai Chi.

Outcome

The number of falls experienced by the participants, and injuries sustained, was obtained for up to 2 to 4 years.

Results

This report has some complicated statistics, but the highlights were as follows:-

• 1,049 controls suffered 1,499 falls, an average of 1.43 falls per person.
• 1,255 treated persons suffered 1,506 falls, an average of 1.20 falls per person.
• the adjusted fall incidence ratio for treatment arms which included general exercise was 0.9 (95% confidence intervals 0.81 - 0.99).
• the adjusted fall incidence ratio for treatment arms which included balance was 0.83 (95% confidence intervals 0.70 - 0.98).
• Tai Chi appeared, on small numbers, to be the best intervention with about a 35% reduction in fall incidence.

Comment

The effect sizes in this study were not large, with effective treatments producing reductions in fall incidence of 10 and 17%, though Tai Chi was notable in being more effective, but in small numbers. These effects, applied to the very large proportion of elderly people in today’s society, would produce very significant benefits in falls and injury avoided, would reduce disability, and would allow considerable health care spending to be applied to more useful ends.

This is an important and interesting public health subject, worthy of more study in UK settings.

Reference:

Evidence-based prevention

The idea that prevention is better than a cure is commonly held by the public and by health care professionals. It makes sense, it seems to be a good thing, and why aren’t “they” spending more on prevention?

There are some outstanding examples of prevention. Smallpox eradication must be the public health triumph of the century, though the apparent success of many vaccination programmes was achieved on the back of incidence rates that had been falling steadily and substantially for decades.

What about telling people not to do things. Does that work, and is there any evidence that it does? A study from the USA [1] indicates that drug prevention programmes targeted towards teenagers can produce meaningful and durable reductions in tobacco, alcohol and marijuana use.

Design

In the Spring of 1985 56 junior high schools in three areas of New York State were assessed to determine existing cigarette smoking levels. From within groups of schools with similar levels of cigarette smoking, schools were randomly assigned to one of three interventions:

1. Prevention programme with a formal 1-day training workshop and implementation feedback.
2. Prevention programme using videos and no implementation feedback.
3. No special intervention.

The prevention programme consisted of 15 periods taught in the 7th grade (12 year olds). The intervention was designed to teach students cognitive behavioural skills for building self-esteem, resisting advertising pressure, managing anxiety, communicating effectively, developing personal relationships, and asserting rights. It was also designed specifically to teach skills and knowledge related to resisting social influences relating to tobacco, alcohol or other drugs.

This programme was followed up in each of two subsequent years (8th and 9th grades) with additional intervention sessions, but not later.

Participants

The original sample was just under 6,000 students who entered the study in 1985. Of these, follow-up information could be obtained on just under 3,600 six years later in 1991. The follow-up sample was 90% white and had a mean age of 18 years in 1991.

A subgroup analysis was also carried out on those students who were judged to have received at least 60% of the intervention programme (high-fidelity sub-group). This comprised 2752 students.

Results

Using data on the whole sample of 3597 students, the effects of both intervention programmes was to reduce cigarette consumption significantly - a reduction of 6% from 33% to 27% using cigarettes in any month. The proportion smoking 20 cigarettes a day was reduced by more than 20%. There was no difference in alcohol use, though problem drinking was reduced significantly by 6%. There were only slight differences in marijuana consumption.

For the high fidelity subgroup, there were significant reductions of 10% in cigarette smoking and 4% reductions in both alcohol and marijuana consumption. Problem drinking and heavy cigarette use in this group were reduced by a third and frequent marijuana use by almost half. The combined use of tobacco, alcohol and marijuana was reduced by 66% in this group.

Viewed by the crude results alone, the gains of prevention interventions may seem modest. However, these results were obtained six years after the intervention, and indicate a powerful and long-lasting effect of an intensive and thorough prevention programme incorporating social skills training. Even modest gains spread over a large population can have immense health gains for society and individuals.

It was notable that in the sub-group which attended more than 60% of the classes the programmes had a much greater impact. Heavy smoking, heavy drinking and polydrug use were reduced by very large amounts - 25% to 66%. These are large gains.
This important study was randomised, was intensive, and had a long period of follow up. It is worth reading by all those involved in the design and implementation of health prevention programmes.

**Social marketing makes a difference**

*Bandolier* has also received a copy of a fascinating report on the usefulness of social marketing on tobacco, alcohol and marijuana use in Canada [2].

The Canadian Department of Health employed several health promotion social marketing campaigns on drugs and tobacco. The campaigns are based on social marketing principles and strategies, which recognise that informing the public about a particular issue will not, by itself, lead to changes in attitude or behaviour. Changing behaviour sometimes requires specific kinds of marketing - social marketing - which attempt to change perceptions, attitudes, opinions and behaviours that underlie an individual’s health or lifestyle habits.

Social marketing employs a mix of traditional marketing tactics including:-

- event marketing/corporate sponsorship
- special promotions
- information, communications and skills development
- advertising
- direct marketing
- public health/media relationships.

Such social marketing campaigns have been used in Canada since 1985/6. The impact has been monitored and the report [2] gives information up to 1992.

**Does it work?**

The graph shows considerable reductions in the use of alcohol, tobacco and drugs by teenagers aged 11-17 between the years 1989 and 1992. It is not possible to ascribe all, or indeed, any, of this fall to social marketing since there would have been many different influences on behaviour. However, this report is worth reading, despite an apparent lack of evidence, if only because of the way that it profiles different teenagers and examined what methods are likely to influence target groups with completely different attitudes to drugs. Well worth a read, especially for those engaged in preventative health campaigns.

**References:**


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**H pylori & ulcers**

*Bandolier* has reported on this topic several times, but there are some new reports which might be helpful to those working on local guidelines or unsure of what to do. These are reviewed briefly.

1. **The use of Helicobacter eradication therapy in the treatment of duodenal ulceration** is a research and development briefing paper by Dr Liam Murray published in March 1995 by South and West RHA. It strongly recommends that all patients with confirmed duodenal ulcers and concurrent *H pylori* infection should receive eradication therapy. It gives a good, short review of the problems and treatments. Nine pages, 17 references. From R&D Directorate, S&W RHA, tel 0117 928 7224/Fax 0117 928 7204.

2. **The management of upper gastrointestinal problems** was published by R&D, Northern & Yorkshire RHA earlier this year. It goes into greater detail in comparing different treatment options. It examines the problem of how to handle patients presenting with upper gastrointestinal disease in general, rather than just those with *H pylori* infections. It is a useful and readable review. Thirty-four pages, 66 references. N&Y RHA tel 01423 500066/Fax 01432 843140.

3. **Helicobacter pylori and peptic ulcer.** A systematic review of effectiveness and an overview of the economic benefits of implementing what is known to be effective. This looks at different treatment types using NNTs, and examines how changes in practice taking account of existing evidence could have a major impact on spending in this area. Fifty-two pages, 68 references. Available from Cortecs Diagnostics, tel 01423 500066/Fax 01432 843140.
With new school terms starting GPs are beginning to see the Autumn rush of children infected with head lice. It was timely that the BMJ published a systematic review of the clinical efficacy of topical treatments for head lice. Busy GPs have asked Bandolier for a short précis of the article.

Methods

The authors set some high standards for searching for studies and including them in their analysis. They even located eleven unpublished trials from Wellcome - comparing malathion and permethrin, though unfortunately the company demanded confidentiality, so they could not be used.

The criteria the authors used for inclusion and exclusion included important general issues like randomisation and blinding, and also a number of methodological issues particular to head lice studies. In the end they included in their analysis seven studies of 21 individual treatments, including placebo and eight compounds. The clinical end-point they chose was absence of viable lice or their eggs at 14 days after (usually) a single application.

Results

Cure rates with treatment with inactive vehicle were about 6%.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cured/Total</th>
<th>Percent cured</th>
<th>NNT (96% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Permethrin 1%</td>
<td>631/647</td>
<td>97</td>
<td>1.09 (1.00 - 1.20)</td>
</tr>
<tr>
<td>Lindane 1%</td>
<td>365/437</td>
<td>84</td>
<td>1.29 (1.16 - 1.45)</td>
</tr>
<tr>
<td>Pyrethrines</td>
<td>183/204</td>
<td>90</td>
<td>1.19 (1.08 - 1.34)</td>
</tr>
<tr>
<td>Carbaryl 0.5%</td>
<td>143/145</td>
<td>98</td>
<td>1.08 (1.00 - 1.18)</td>
</tr>
</tbody>
</table>

With active treatments they were higher, often above 80%. However, only permethrin 1% creme rinse showed efficacy in more than two studies with a lower 95% confidence interval of cure rate above 90%. In the table the data from the trials has been aggregated to show the number of patients treated and treated successfully to yield an average cure rate and NNTs. This supports the conclusion that the treatment of choice is permethrin at 1% strength with the lowest NNT (approaching 1) in the largest group of treated individuals.

Reference:


Evidence-based patient choice

One of the objectives of Bandolier is to promote evidence-based health care, and the components of evidence-based health care are summarised in the diagram. There are, of course, many other topics not specifically mentioned in the diagram which are components of evidence-based health care - for example evidence-based audit and screening.

Evidence-based consumer choice

In evidence-based “patient choice”, women who are pregnant are not patients and information for them should probably be called “evidence-based consumer choice”. There are other examples, for instance about evidence-based eating for health, where the target is not a patient, but a member of the public.

A landmark in consumer choice was reached with the publication of the first edition of “Effective Care in Pregnancy and Childbirth” in 1989. This was a book for consumers based on “a systematic hand search of over 63 journals from the 1950s onwards” and a survey of “over 40,000 obstetricians and paediatricians in 18 countries in an attempt to identify unpublished studies”.

The result of this major effort was a 15,000 page book in two large volumes - “Effective Care in Pregnancy and Childbirth”, and the regularly updated electronic database of systematic reviews - the Cochrane Pregnancy and Childbirth Database [1].

The second edition of this book has now been published [2] and is excellent not only for women who are pregnant but also for anyone interested in evidence-based health care. This is in part because of its approach, in part because of
Evidence Based Health Care (EBHC)

EB Patient Choice
EB Clinical Practice
EB Public Choice
EB Purchasing
EB Education and Training
EB Research
EB Health Service Management
General Hospital
Mental Health
Learning Disability
Primary care
Screening
the appendix which gives a very clear classification of different forms of care. It groups different forms of care into six different forms, those which are:

- beneficial
- likely to be beneficial
- with a known trade-off between beneficial and adverse effects
- of unknown effectiveness
- unlikely to be beneficial
- likely to be ineffective or harmful

The review of the first edition said that “there are few books that should be considered as essential reading in obstetrics, but this is certainly one of them”. It could well be said that there are few books that can be considered as essential reading in evidence-based health care, and this is certainly one of them.

References:

Stocking filler


Genetics can be like video recorders - dead easy for a nine-year old, but more difficult for the forty-something parents. The pace of change has been so great that even relatively new graduates of science or medicine see their knowledge rapidly being made redundant. What hope for the rest of us?

Perhaps not much, but with books like this one, there is some hope of keeping up. It is the result of a collaboration between one of the UK's most distinguished scientists and the science correspondent of the Observer. The result is an immensely interesting and readable book which makes the journey along the road carved out by the new genetics relatively painless.

The key to this book is that each new twist in the spiral is illuminated by real examples - of patients and their problems, from history and from pre-history. Like many good things it is people orientated, so that the science and the medicine become part of their human perspective. Some of the scientific nuance may be lost in this, but it gains so much more from being accessible to all.

Those of us of a certain age who were galvanised by Jim Watson’s story of the discovery of the structure of DNA - The Double Helix - will recognise the same sort of feelings being engendered with The Book of Man. It is a book for every age, from the precocious 11-year old to their grandparents. It could also be a useful aid in helping to inform patients with genetic problems come to terms with the knowledge about themselves. Definitely one for the bookshelf.