DVTS AND ALL THAT

We get much information about the dangers of deep vein thrombosis (DVT) with air travel, about not drinking too much alcohol, keeping hydrated, taking a walk or doing exercise, and taking an aspirin before we fly. Some evidence helps. One systematic review looks at the incidence of DVT in the general population [1], while another [4] calculates the NNT of aspirin to prevent one DVT while flying.

Systematic review

Several databases were searched to 2001 for articles on the incidence of DVT and thromboembolism. Studies reported all diagnosed patients in a defined general population in a developed country. DVT diagnoses had to be confirmed by clinical tests (like a scan) or a satisfactory validation study of the accuracy of the diagnosis performed. The age range had to be specified, so incidence rates could be calculated per 100,000 person years. For the purposes of the review, DVT cases had to be new and not to be recurrent, combined with pulmonary embolism, and due to any cause.

Results

Finally accepted were nine studies from a combined population of about 19 million persons published since 1976. Most studies were conducted in Sweden or the USA.

Incidence rates adjusted to include only new DVTs, due to all causes, and for all ages of the population are shown in Figure 1. Most studies clustered around an incidence of 50 per 100,000. DVT occurred rarely below 20 years, but in...
creased with age (Figure 2), so that in over 70s the rate was 200 per 100,000. Incidence was about the same in men and women.

The causes of DVT were attributed to cancer or previous hospital admission, for about a quarter to a third of cases for each cause. About 40% of cases of DVT had no known cause.

Risk factors for DVTs

A reasonably large case-control study in France [2] examined 636 patients presenting with DVT and paired them by age and sex with a control group of patients presenting with influenza or rhinopharyngeal syndrome. DVT had to be documented by at least one objective test. Risk factors were classified as intrinsic or permanent, and triggering or transient.

In 988 patients who had not undergone surgery or had a plaster cast on the lower extremity during the preceding three weeks, a number of intrinsic and triggering factors were associated with a higher risk of DVT (Table 1). Odds ratios of about 3 or above were found for a previous history of DVT or pulmonary embolism, venous insufficiency and chronic heart failure, with pregnancy, violent effort or muscular trauma, deterioration in general condition and being confined to bed or armchair as the main triggers.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Case patients (%)</th>
<th>Control patients (%)</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intrinsic factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of DVT or embolism</td>
<td>21</td>
<td>2.4</td>
<td>16</td>
</tr>
<tr>
<td>Venous insufficiency</td>
<td>70</td>
<td>41</td>
<td>4.5</td>
</tr>
<tr>
<td>Chronic heart failure</td>
<td>10</td>
<td>4.5</td>
<td>2.9</td>
</tr>
<tr>
<td>BMI more than 30</td>
<td>15</td>
<td>7.0</td>
<td>2.4</td>
</tr>
<tr>
<td>Standing more than 6 hours/day</td>
<td>39</td>
<td>32</td>
<td>1.9</td>
</tr>
<tr>
<td>More than 3 pregnancies</td>
<td>17</td>
<td>9.8</td>
<td>1.7</td>
</tr>
<tr>
<td><strong>Triggering factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy</td>
<td>2.4</td>
<td>0.3</td>
<td>11</td>
</tr>
<tr>
<td>Violent effort or muscular trauma</td>
<td>7.9</td>
<td>1.0</td>
<td>7.6</td>
</tr>
<tr>
<td>Deterioration in general condition</td>
<td>6.3</td>
<td>1.2</td>
<td>5.8</td>
</tr>
<tr>
<td>Immobilisation</td>
<td>8.0</td>
<td>2.0</td>
<td>5.6</td>
</tr>
<tr>
<td>Long distance travel</td>
<td>13</td>
<td>6.3</td>
<td>2.4</td>
</tr>
<tr>
<td>Infectious disease</td>
<td>19</td>
<td>13.0</td>
<td>2.0</td>
</tr>
</tbody>
</table>

Table 2: Significant associations with DVT

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Case patients (%)</th>
<th>Control patients (%)</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>48</td>
<td>34</td>
<td>1.4 (1.1 to 1.9)</td>
</tr>
<tr>
<td>History of DVT</td>
<td>12</td>
<td>4.4</td>
<td>2.7 (1.2 to 6.3)</td>
</tr>
<tr>
<td>Obesity</td>
<td>34</td>
<td>20</td>
<td>1.7 (1.2 to 2.5)</td>
</tr>
<tr>
<td>Recent travel</td>
<td>24</td>
<td>7.5</td>
<td>3.3 (1.8 to 6.0)</td>
</tr>
</tbody>
</table>

Travel as a risk factor

Another case-control study from France examined this issue [3]. It used all patients admitted for DVT or pulmonary embolism from 1992-1995, with control patients those admitted for an event other than these. Since it was a cardiology department, these were mostly chest pain, hypertension and syncope. There were 160 cases and controls.

Cases and controls were well matched for age (mean 66 years), but there were more women in the cases (Table 2). More of the cases were obese (not defined in this paper), had a history of venous thromboembolism, or had made a journey lasting more than four hours in the preceding four weeks.

Of the 39 cases who had made a long journey, 28 made it by car, nine by plane and two by train. The mean journey length was about six hours for each mode of travel, and the average time between journey and occurrence of symptoms was 13 days, but with much variation. For 29 of the 39 cases there was no other circumstance or disease to explain the event.

Flying and aspirin for DVT prevention

Is there any way to assess the benefit of taking aspirin to prevent DVT in a long distance flight? One study has attempted to do that [4].

It took the risk of DVT as being about 20 per 100,000 travellers for one long distance journey a year, based on a British Parliamentary Select Committee estimate of the risk as being 0-40 per 100,000 travellers. Other literature suggests this to be a reasonable figure, but the authors used a range of estimates of 10-40 per 100,000 to represent different levels of risk, like age.

The potential benefit of aspirin was a risk reduction of 29% for 160 mg of aspirin daily for 35 days from a 13,000 patient study of aspirin after hip fractures.

Table 1 shows the results in terms of numbers of patients needed to be treated with aspirin to prevent one of them having a travel-related DVT. Estimates range from 8,600 at high risk, to 34,000 for low risk.
Comment

DVT is uncommon, and especially uncommon in people without recent cancer or previous hospital admission. With these conditions it is 50 per 100,000 per year, and without them it is about 20 per 100,000 per year. Being older, having certain medical conditions, and having a BMI over 30 increase the risk. Long journeys also increase the risk. The risk is still about 1 in 5,000 in the general population, and that sort of risk is attributed to long distance air travel. To put it in perspective, the risk of being killed on the roads in the UK is about 1 in 17,000 each year.

Aspirin, or stockings, may help, but lots of people have to take aspirin for one to be helped. We don’t know what dose, and for how long, is effective. We don’t know how effective it would be, and we don’t have a good handle on how potential harms relate to potential benefits.

Despite a low risk to the individual, there are a lot of travellers by car, rail and air. At peak levels, Heathrow airport handles about 250,000 travellers a day, many on long flights. Even a low incidence of travel-related DVT should impact on the overall incidence of DVT. But studying benefits of any intervention will not be easy given the enormous size needed for any study. In the meantime the advice we are given for air travel might be applied to other forms of travel or behaviour.

References:

Table 3: Numbers needed to treat with aspirin to prevent one DVT, at different levels of risk

<table>
<thead>
<tr>
<th>Per 100,000 travellers or travellers treated with aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated risk of travel-related DVT</td>
</tr>
<tr>
<td>Number of travel-related DVTs prevented by aspirin</td>
</tr>
<tr>
<td>Number of travel-related DVTs occurring despite aspirin treatment</td>
</tr>
<tr>
<td>NNT with aspirin to prevent one additional travel-related DVT</td>
</tr>
</tbody>
</table>

MINDSTRETCHER - CHECKING OUT SYSTEMATIC REVIEWS

Who guards the guards? Well, actually, we have to when it comes to systematic reviews. We can have good trials, and bad trials, and good reviews and bad reviews. We can also have any combination of these (Figure 1), with different consequences. A bad review of good trials may tell us where the literature is, or at least be a start. A good review of bad trials may tell us what characteristics a good trial should have.

But for the rest it is confusing, and the only defence is a little knowledge, a healthy dose of suspicion, and enough energy to rub a few neurones together. A recent product of HTA [1] helps in refining some of the factors we know or suspect can give rise to bias in systematic reviews.

Study

The raw materials were meta-analyses based on comprehensive literature searches providing sufficient data and information on techniques used to allow replication of the meta-analysis. A comprehensive literature search was one not confined to English, used the Cochrane Library or at least two other databases and had an indicator that unpublished trials had been sought.

Each of 159 meta-analyses was recalculated to produce a statistical outcome like relative risk. A variety of sensitivity analyses were then performed for different characteristics of trials. The results were expressed as the ratio of a statistical outcome like odds ratio between trials with one characteristic and those with another, a ratio of estimates.
Results

One interesting but important result was that the correlation between statistical results in the reports and the recalculated results was close to perfect. The analysis then went on to examine the impact of a number of important factors, summarised in Table 1.

Unpublished reports

There were 630 published trials and 153 unpublished trials. Unpublished reports were less likely to be double blind. Overall, there was no difference between published and unpublished trials, and the ratio of estimates was 1.1 (95% confidence interval 0.98 to 1.15). If anything, unpublished trials tended to be less beneficial than published trials.

Language of publication

There were 485 English language trials for analysis and 115 in other languages. Reports in languages other than English were less likely to be double blind. Overall, non-English language trials had a more beneficial effect than English studies, with a ratio of estimates of 0.84 (0.74 to 0.97).

Publication in non-MEDLINE journals

There were 580 trials published in journals indexed by MEDLINE, and 161 published in journals not so indexed. There was no difference in the proportion properly randomised and blinded. Overall there was no difference between trials from indexed journals and non-indexed journals, with a ratio of estimates of 0.94 (0.82 to 1.07).

Concealment of allocation

Concealment of allocation here means that the trial is not only randomised, but that researchers have no knowledge of what treatment the next patient will have. Adequately concealed trials will usually have central randomisation, coded drug packs, or assignment envelopes, while inadequately concealed trials use alternation, date of birth, or open random number tables, for instance. It combines randomisation with some elements of blinding.

There were 118 trials with adequate concealment, and 186 in which concealment was inadequate or unclear. Those trials with inadequate or unclear concealment had a more beneficial effect (ratio of estimates of 0.79; 0.70 to 0.89).

Double blinding

There were 237 double blind trials, and 162 not double blind. Overall those trials not double blind tended to have a more beneficial effect, but the ratio of estimates of 0.88 (0.75 to 1.04) did not reach statistical significance.

Comment

There’s not much here that we didn’t know, but this is perhaps a larger examination of some of these issues than has been done before. It is complicated by issues like whether differences persist when only high quality trials are used. The authors examine this, and by and large they do. But it is a bit circular, and applies only to published or unpublished studies, language and journal of publication.

Any analysis like this is a melange of trials of different interventions in different conditions, and, sometimes, the validity of trials included in meta-analysis can be poor. The amount of data available is also an issue. So we always need to consider a number of issues when looking at a meta-analysis:

♦ How good is the searching? If only English language papers are included, some very good material could be missed. Any attempt to find unpublished material is a bonus, but only with stringent inclusion criteria.
♦ Are the trials randomised, and are they randomised properly? Many reviews do not accept improperly randomised trials. If you read a review that has poor or non randomised studies, see if there is a sensitivity analysis, and if not put it in the bin.
♦ Some studies can be blind, and properly double blind to patient and observer. If unblinded or open studies are included when there are blinded ones available, don’t read on.

It really isn’t that difficult, but it is always comforting that someone has burnt the midnight oil to confirm what we thought we knew.

References:

A major problem with the old chestnut of publication bias is that of knowing what information is actually unpublished. The argument is that systematic reviews come to positive conclusions only because there is a host of negative reports that are unpublished because they are negative. An additional complication comes from the fact that much of that which is unpublished is of inferior quality. How then is it possible to know whether unpublished data is likely to change the magnitude or direction of any result?

Unless we have published and unpublished studies of equal quality, examining the same outcome, the same intervention in the same population, we have little hope of coming to a satisfactory conclusion. A new analysis of the association of dyspepsia with NSAIDs [1] addresses this issue by comparing published data with unpublished data submitted to the FDA.

Study

Randomised trials of NSAIDs and gastrointestinal toxicity were sought through searches of four electronic databases up to the end of 1997. Any oral NSAID administered for at least four days to adults and compared to placebo was considered if it reported gastrointestinal side effects. The analysis was limited to dyspepsia because this outcome is frequently reported in randomised trials.

All FDA reviews of new drug applications and supplements for naproxen, ibuprofen, diclofenac, etodolac and nabumetone were examined because they were the most frequently prescribed NSAIDs in the USA. Each was searched for randomised trials with the same inclusion and exclusion criteria as for published trials. The possibility of studies being in both domains was examined.

After a literature review, a working definition of dyspepsia was made. This was any outcome terms that related to epigastric or upper abdominal pain or discomfort, and including the term dyspepsia, but specifically excluding nausea, vomiting or heartburn.

Treatment and control group percentages and risk ratios were pooled using a random effects model. A meta-regression analysis was also conducted to determine whether the effect of an NSAID was published or an FDA submission, and also examining age, patient type, exclusion criteria, study reporting quality, and dose and duration.

Results

After excluding studies for various reasons, there were 15 reports (1,455 patients) comparing NSAIDs to placebo and with dyspepsia as an outcome in the published literature. There were 11 comparable reports (2,368 patients) in the FDA reviews. All were randomised, almost all were blinded, and 90% of the published and 80% of the FDA studies had quality reporting scores of 3 out of a possible 5, a level known to minimise bias.

The association of NSAID with dyspepsia in published and unpublished studies was the same (Table 1). This analysis included all doses (high, medium or low, which for ibuprofen was more than 3,200 mg for high, 1,600-3,200 mg for medium, and below 1,600 mg a day). In the meta-regression only dose was related to the rate of dyspepsia, with high dose associated with more than twice the rate of dyspepsia. Being a published or FDA study made no significant difference.

Table 1: Dyspepsia and NSAIDs - published and unpublished studies

<table>
<thead>
<tr>
<th></th>
<th>Number of Studies</th>
<th>Percent with dyspepsia (95% CI)</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients</td>
<td>Treatment</td>
<td>Placebo</td>
</tr>
<tr>
<td>Published studies</td>
<td>11</td>
<td>2368</td>
<td>4.1 (2.3 to 5.8)</td>
</tr>
<tr>
<td>FDA studies</td>
<td>15</td>
<td>1455</td>
<td>5.5 (3.1 to 7.9)</td>
</tr>
<tr>
<td>All studies</td>
<td>26</td>
<td>3923</td>
<td>4.7 (3.3 to 6.2)</td>
</tr>
</tbody>
</table>

References:
There has been a sort of received wisdom that it is impossible to say anything about the relative efficacy of two different interventions for the same condition unless they are compared directly in head-to-head randomised controlled trials. There will be circumstances where that may well be true, but an important new study [1] indicates that indirect comparisons are likely to be just as good in most cases.

The problem

If we have trials of treatment A versus placebo and treatment B versus placebo, are we able to make any comment on how good treatment A is compared to treatment B, without a trial that directly compares treatment A versus treatment B?

The argument against might well take the form that these were different trials, with different randomisation, and perhaps in patients with different severity of disease at baseline, conducted over different periods of time, and in which different outcomes may have been measured. There may also be reservations about the amount of information available, because with smaller numbers the possibility that the random play of chance may affect the results would inevitably be greater. Any or all of these should invalidate indirect comparisons.

These are important and valid arguments. But if we have trials in which we know the severity is the same or very similar, conducted over the same time, using the same outcome reported in the same way, and we have large enough amounts of information, might we not then be allowed to draw some conclusions?

Figure 1: Indirect and direct comparisons

The study

There were 44 direct and indirect comparisons available for analysis from 28 meta-analyses. The relative risk for the direct comparison (A versus B) was compared with an imputed relative risk of A versus B from studies of A and B versus a common comparator. For some trials an odds ratio, and for others mean differences, were available.

Results

In general, relative risks were the same for direct or indirect comparisons (Figure 1). Most of the results were similar in terms of positive, negative or non-significant effect, with 32 of 44 indirect comparisons giving the same result as the direct comparison. Of the 12 that were discrepant:

♦ eight involved sample sizes so small as to make any conclusion suspect,
♦ two involved minor changes to a confidence interval either side of 1, thus changing a statistical rather than any clinical conclusion,
♦ one was related to analysis of different doses,
♦ one was possibly a really different conclusion.

By another calculation of discrepancy, the authors indicate that three comparisons may be showing different answers, though of these one was related to analysis of different doses, and the other two could also have dose differences as complicating factors.

Comment

Here we have a clear answer to our problem. Indirect comparisons usually agree with direct comparisons. The dangers come from doing something daft, which means using trials of poor quality, or trials that look at different people, with different entry criteria, or different outcomes, over different periods of time, or comparing different doses.

The critical factor for many will be the dose or intensity of an intervention. Many meta-analyses seem to think that different doses of drugs or intensities of intervention, or clinical situations, can be combined with impunity. That defies experience and logic, and is stupid.

The bottom line here is that in the absence of very large direct comparisons, well performed meta-analyses of indirect comparisons are perfectly acceptable, but only when we compare similar interventions, in similar patients, with similar outcomes, measured over similar periods of times. If we don’t have that, then mistakes could be made.

References:
TOPICAL NSAIDs

It is always interesting when there is a debate about whether an intervention works or not. Often that debate then extends into whether the intervention is worth using or not. One of the best examples is the debate over topical NSAIDs, where despite having a systematic review [1], doubts remain. There are two arguments used to discredit the review. One is that it is “just the rubbing” that produces pain relief. The other is that there must be masses of negative unpublished information that, if we had it, would change the conclusion.

Systematic review

The review searched several electronic databases and a specialist database of trials with pain as an outcome developed by hand-searching journals, and that was subsequently included in the Cochrane Library. Pharmaceutical companies in the UK were also asked for any unpublished studies. Included trials had to be full journal publications of trials that were both randomised and double blind, and with placebo or active comparators.

Acute conditions were defined as sprains or strains, and for these the outcome was one that equated to at least half pain relief after one week. Chronic conditions were predominantly single joint arthritis or rheumatological disorders with the same outcome equating to at least half relief at two weeks.

Results

Overall 86 randomised trials with 10,160 patients were found. Over 75% of placebo-controlled studies had a quality score of 3 out of 5 on a popular scale, known to be associated with minimisation of bias.

Acute conditions

There were 40 trials in strains and sprains with 1,747 patients treated with topical NSAID and 1,492 with placebo (Figure 1). Topical NSAID was better than placebo, with an NNT at one week of 3.9 (95% confidence interval 3.4 to 4.4); 71% of patients had a successful outcome with topical NSAID and 38% with placebo. Topical preparations of ketoprofen, felbinac and ibuprofen had NNTs of 2.6 to 3.5. There were few local or systemic adverse effects, or withdrawals, and no difference between NSAID and placebo.

Chronic conditions

There were 13 placebo-controlled trials in chronic conditions with 547 patients treated with topical NSAID and 550 with placebo (Figure 2). Topical NSAID was better than placebo, with an NNT at two weeks of 3.1 (2.7 to 3.8); 65% of patients had a successful outcome with topical NSAID and 30% with placebo. There were few local or systemic adverse effects, or withdrawals, and no difference between topical NSAID and placebo.

Topical versus oral NSAID

Five studies compared topical with oral NSAID, with no benefit of oral over topical treatment (three in acute and two in chronic conditions).

Comment

So is it just the rubbing? A simple look at the two L’Abbé plots (Figures 1 and 2) tells us that cannot be the case. In these trials, most of which we know had matched placebo, the only difference is that one version of the gel or cream had NSAID in it. Topical NSAIDs produced about twice the effect of placebo, despite any rubbing that took place with topical NSAID or placebo.
What about unpublished material? This review uncovered previously unpublished trials, with about 17% of the total unpublished, so it was hardly ignored. And the message from an HTA report is that unpublished and published information do not differ in their conclusions, and we now know funnel plots to be unhelpful in finding publication bias [2].

So we have known efficacy with known safety against the gastrointestinal harm associated with oral NSAIDs [3]. There may still be arguments about whether these topical preparations are worth using, and particularly in which patients with chronic conditions they will work best. But is there room for argument about whether they work?

References:

Topical help

Pain Research at Oxford is undertaking to update systematic reviews on topical NSAIDs in acute and chronic conditions, and to add to them a review of rubefacients. Extensive searching of electronic databases and reviews is being supplemented with requests about published and unpublished trials to pharmaceutical companies around the world.

Given the arguments that surround these products, you can help. Rather than wait for the review to be finished, please send comments about trials, or reviews, or questions you would like to see answered so they can be incorporated into the review process.

NRT OTC

An important message is that nicotine replacement therapy (NRT) obtained over-the-counter (OTC) from pharmacies works as well as that obtained by prescription [1]. An extensive search strategy looked for randomised studies comparing OTC NRT with placebo, and OTC NRT with prescription NRT.

Results

Four randomised trials studied 2,290 subjects over 2.5 to six months with slightly different definitions of quit rates. Pooled quit rates were 9.6% with OTC NRT and 4.0% with placebo (Figure 1). The pooled relative benefit was 2.4 (1.7 to 3.3), and the number needed to treat for one person to quit smoking was 18 (13 to 29).

Of four controlled studies of OTC NRT versus prescription NRT with 9,307 subjects over six to 12 months only two were randomised. Pooled quit rates were 8.9% with OTC NRT and 8.1% with prescription NRT (Figure 1). The pooled relative benefit was 1.1 (0.9 to 1.3), showing no difference.

Figure 1: OTC NRT versus placebo (open circles), or OTC NRT versus prescription NRT (filled circles)

Comment

There are a number of methodological issues in this meta-analysis. It makes useful reading, though, especially in relation to arguments about whether OTC NRT is less effective than prescription NRT, and about the absolute efficacy of NRT. There seems to be no difference, and that with NRT about 10 smokers in 100 will stop smoking with NRT, about twice as many as without it.

References: