

SAFETY UNDER THE SPOTLIGHT

Issues surrounding safety, both of patients and pharmacists, were key themes of the 7th congress of the European Association of Hospital Pharmacists held in Vienna from 20 to 22 March. Christine Clark reports



Vienna: the Michaelertor entrance to the Hofburg complex, venue of the EAHP congress

Reporting of safety information in randomised controlled trials (RCTs) is often neglected, said Professor JOHN IOANNIDIS, University of Ioannina School of Medicine, Greece, in his keynote address to the congress. Often, there is less space for information about product safety, such as whether or not adverse events or side effects have been reported, than that allowed for the list of authors, he lamented.

A study conducted by Professor Ioannidis has shown that in HIV, and in seven other important areas, safety issues are poorly reported. He had examined the factors that appeared to influence safety reporting. It improves if a trial involves dose comparisons but is worse if the report is published in journals with an impact factor greater than 7 (the impact factor being the number of times that articles from the journal have been cited in the past two years divided by the total number of articles published by the journal in that time). If the medicine in question has already been used for a different indication, then safety appears to have low priority, and if a significant positive effect is demonstrated, then safety appears to be even less important.

The next logical question is whether the information concerning safety is retrievable or whether it has ever been collected in the first place. To answer this question, Professor Ioannidis had examined RCTs concerned with the treatment of acute sinusitis, for which antibiotic treatment was probably unnecessary. He had written to all the trialists

involved over a 10-year period and asked for two pieces of information: (1), the number of participants who had developed nausea and vomiting that had required hospitalisation and (2), the number in whom treatment was discontinued because of toxicity, and the duration of the toxicity. Of the 38 trialists, 16 had responded, of whom nine were able to give data. Of the seven unable to give data, this was because none had been collected (two), the database had been lost (three), and in the remaining two cases, the database had been sold or relocated. Only four of the others were able to give data on the number of days of toxicity. Their results suggest that publication in a general medical journal and non-industry sponsorship are two factors that improve the chances of data retrieval. Professor Ioannidis noted that despite the randomisation of more than 7,000 patients, the results of the trials had, in any case, been equivocal.

There are numerous sources of heterogeneity for safety data, he said. These include:

- 1 use of concurrent medications
- 1 the mode of collection of the safety data
- 1 variable durations of treatment and/or safety surveillance
- 1 the use of blinded trials (especially of patients)
- 1 selection criteria for patients
- 1 intention-to-treat analysis versus per-protocol analysis

Evidence-based medicine involves the systematic scrutiny of available data in contrast to simple acceptance of expert opinion or unchallenged tradition. It is also concerned

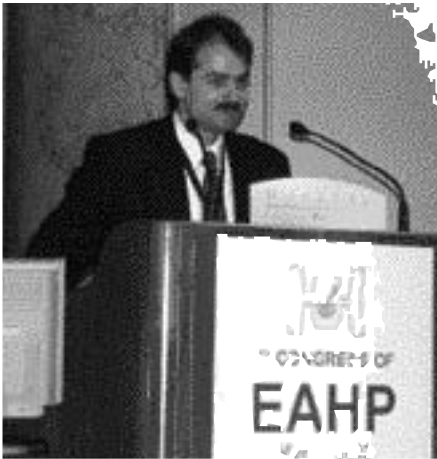
with issues that matter in patient care and with the dissemination of good practice.

More than one million RCTs have now been conducted in the 54 years since the first one was performed. Now, systematic reviews offer a way of putting that information into order and meta-analyses represent a means of extracting some quantitative information from the masses of published data.

A major problem lies in deciding which information about medicines to trust, he suggested. Experts rarely agree and it is difficult to get an evidence-based opinion from them. Guidelines are not necessarily evidence-based, and pharmaceutical products are often not promoted on the basis of evidence. Reviews, both traditional and systematic, try to make some sense of the available material. Many people place considerable reliance on the internet, he added.

In 1993, a study had examined the numbers of Medline reports compared with the numbers of patients. For example, for the spongiform encephalopathies, there had been 2,050 reports per 1,000 patients. This raised the question of the pertinence of evidence. Another study targeted 154 important interventions used in the treatment of 14 haematological malignancies. The authors found 783 RCTs concerned with treatments for these conditions, and these provided an evidence base for 37 of the 154 decisions. Furthermore, when the data were applied prospectively, they showed that in 255 consecutive patients, more than 50 per cent of the management decisions were not supported by RCT evidence.

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John Ioannidis: Can we be fooled by large amounts of accumulated data?

In some areas, there is a lot of evidence, and in others there is very little, he said. Meta-analyses increase the power of experimental evidence by bringing data together. One of the issues in meta-analysis is the diversity or heterogeneity of trials. It is also necessary to identify sources of bias.

It may be important, he said, to recognise areas in which no more evidence is now needed. An example is trials of dexamethasone for chemotherapy-induced emesis. The results of individual trials are unconvincing but a cumulative meta-analysis of the trials had shown that an unequivocal, positive effect was evident after 300 patients had been randomised. In the event, more trials have been carried out — eventually involving a total of 3,000 patients.

There are several important challenges in meta-epidemiology, said Prof Ioannidis. These were:

- 1 randomised versus observational studies;
- 1 large versus small studies
- 1 early versus late evidence (“when can we be certain?”)
- 1 safety versus efficacy
- 1 challenges beyond classic therapeutic interventions

Turning first to the question of RCTs versus non-randomised observational studies (NROSs), Professor Ioannidis reminded the audience that the RCT, in theory, has fewer biases than the observational study. In 2000, two studies had examined RCTs and observational trials that had tackled the same questions. They had shown that the results were concordant, but that, if anything, RCTs showed evidence of greater heterogeneity. The authors had concluded that both designs of trial worked.

Heterogeneity, or diversity, of results is usually a greater problem with NROSs than with RCTs, said Professor Ioannidis. In one series, there was significant heterogeneity in nine out of 32 RCTs compared with 13 out of 32 NROSs. The results are more diverse with NROSs and more complete with

RCTs, he summarised. Furthermore, trial results are generally more favourable with NROSs and tend to be more conservative with RCTs, although there can still be large differences in the magnitude of effect size. Discrepancies of 50 per cent between trials are not uncommon. Both types of study design have their place and they should not be seen as mutually exclusive, he suggested.

A critical question in this arena is, “Does evidence change over time?” or, put differently, “Can we be fooled by large amounts of accumulated data?” Trials with positive results tend to be published before those with negative results. A review of trials at the National Institutes of Health in the US has shown that positive trials are published earlier. Positive trials are defined as those in which the results reach statistical significance, “the holy grail of $P < 0.05$ ”, said Professor Ioannidis. The effect of this is that early reports of any intervention tend to be optimistic. Positive and negative trials take the same length of time to complete, but publication is the problem because an effective intervention has major financial implications. The publication of trials in which the results are equivocal is generally delayed. The use of anticoagulants in myocardial infarction illustrates some of these points. If the effect sizes (as odds ratios) are plotted against time, then the early results from several NROSs suggest a large effect, but when RCTs are performed later, the effect is shown to be much smaller.

There have been two big surprises in the treatment of myocardial infarction, concerning the use of nitrates and magnesium. In each case, early studies suggested that they are an effective intervention. For magnesium, trials involving more than 2,000 patients have been undertaken. Eventually, the ISIS IV trial showed that neither magnesium nor nitrates is effective. “We have been fooled by substantial amounts of evidence”, said Professor Ioannidis.

— GUIDELINES

The next topic that Professor Ioannidis addressed was guidelines and the extent to which they made use of the available evidence. “Very few guidelines use evidence from systematic reviews or meta-analyses”, he said. One study had evaluated 192 sets of guidelines published in peer-reviewed journals. Approximately half of these had dismissed the available RCT evidence.

One of the big remaining challenges is RCTs of interventions to reduce the number of medical errors. So far, only 13 have been published and the sample sizes ranged from 107 to more than 4,000. Two features stand out: first, the error rates in control groups are unexpectedly large — 10–63 per cent; second, there are large benefits from simple interventions such as strict protocols or reminders.

The association between genetic markers and disease outcomes is something to watch. Early reports of such associations are often disproved as more data becomes available, although the opposite can also happen. The smaller the first study, the greater the chance that the result is wrong, he warned.

In conclusion, Professor Ioannidis said that evidence-based medicine can give us some answers but is best at creating new questions and helping to develop a critical approach. Evidence, he said, is not simply numbers, but must be interpreted with intelligence.

— CYTOTOXICS

Occupational exposure to cytotoxics for ward personnel is an issue that should be tackled, according to Dr JOHAN VANDENBROUCKE (University Hospital, Ghent, Belgium). Up to 30 per cent of intravenous bags have surface-contamination with cytotoxic agents, he said. When bags are “spiked” for administration, leakage is common and there is leakage in every case, when sets are disconnected. This can either be tackled by extensive use of protective clothing or by using dry connection systems (that prevent the leaks). Dr Vandembroucke and his colleagues have developed a cytotoxic administration set (CAS) that uses the dry connection approach. There are two essential components to this, namely a “break-away” (BAW) seal in the administration port and a female Luer lock at the end of the outlet tube. Instead of being spiked, this is connected to an administration tube with a male Luer end. Only when the connection is made is the BAW broken, allowing the cytotoxic solution to flow. Before the set is disconnected the line must be flushed. There can be as much as 20ml solution left in the tubing and this can be a significant proportion of the dose, explained Dr Vandembroucke. Experiments in his laboratory have shown that a minimum of 75ml is needed to flush effectively, and so, in his hospital 100ml is used routinely. For paediatric patients, a smaller flush volume (50ml) can be used if the volume in the drip chamber is reduced to 2ml. Dr Vandembroucke’s department has also developed procedures for bolus injections, intrathecal injections and for bladder instillations using cytotoxic agents. Furthermore, they have a safe method for dissolution of cytotoxic capsules, which, in the past, nurses used to open.

Isolators are excellent engineering controls — but only if they are run by robots, according to Dr COLIN DAVY (specialist inspector, Health and Safety Executive, UK)

A study carried out recently in the UK had been designed to gather information about occupational exposure to cytotoxic agents. Subsidiary objectives had been to monitor changes in working practices, to inform the debate surrounding the use of positive and negative pressure isolators and to investigate the efficiency of the systems.



Johan Vandembroucke (left) and Colin Davy taking questions from the floor during a session discussing occupational exposure to cytotoxics

Two sites were used for the study. The first was a cytotoxic reconstitution unit equipped with a flexible-skin, positive pressure isolator that was used for preparation, sterilisation and storage. Personal protection equipment was also in use, noted Dr Davy. Over a period of four days, urine samples were collected, the operators' breathing zones were monitored and wipe samples of surfaces were taken. The results showed that urine platinum levels were elevated, as were the levels in the operators' breathing zones. When compared with typical roadside levels of atmospheric platinum (released from catalytic converters), the levels were considerably higher. Wipe samples of surfaces and glove samples showed variable levels of contamination with ifosfamide, cyclophosphamide, cisplatin and methotrexate.

The second site used a negative pressure isolator sited in a clean room. Again, the results showed contamination of operators' urine with platinum and contamination of air in the breathing zones. All samples taken from gloves and from the floor showed contamination with cytotoxic agents. Overall, said Dr Davy, this gave a picture of low level contamination and low level drug absorption. This was not related to the volume of drugs prepared. In this study, contrary to expectations, platinum absorption appeared to be greater where the negative pressure isolator was used. This might have been due to a problem with the product, suggested Dr Davy.

In the discussion that followed, Dr Vandembroucke remarked that a recent French study had shown approximately four times as much cytotoxic contamination around an isolator as there was around a biological safety cabinet. This was presumed to be because the operators believed they were protected and were therefore less careful to avoid splashes and leaks.

Asked whether there are any European guidelines about the rotation of staff working with cytotoxic agents, Dr Vandembroucke said that this is forbidden in Belgium because it spreads the risk. As there are no safe levels for cytotoxic agents, it is not acceptable to spread the risk, and it is

recommended that a small number of well-protected staff should work with them. Rotation of staff is permitted, to prevent stress and for reasons of economy, he added.

Another member of the audience asked whether charcoal filters would improve the performance of recirculating isolators. Dr Davy said that work on this topic is ongoing at the University of Bath. Dr Vandembroucke said that work in Germany has shown that activated charcoal adsorbed cytotoxics in proportion to their concentration in the air and, when the ambient concentration falls, there is a risk that the filter will give up the adsorbed drugs again. Therefore, charcoal filters would only be useful if they could be regenerated daily.

— DOSE-BANDING

Dose banding of cytotoxics reduces wastage and results in only minor differences in dosage compared with the traditional method, concluded FIONA McLEAN (senior oncology pharmacist, Western General Hospital, Edinburgh). Dose banding is a system in which doses are rounded up or down to pre-determined standard doses, instead of calculating individual doses based on body surface area (BSA). The rationale for this is that the original formula for BSA was derived from a sample of only nine patients and is therefore inherently inaccurate, explained Ms McLean. The dose-banding project had been agreed with the director of oncology and five drugs — fluorouracil, cyclophosphamide, methotrexate, folic acid and epirubicin were selected. All five were in frequent use, were stable in syringes and were commercially available in pre-filled syringes. Criteria for banding were established for each drug and an explanatory poster was designed for the wards. The results showed that doses deviated by 5 per cent or less from the doses that patients would have received using the individualised method and that there was a faster turn-round time in the pharmacy. Wastage was also reduced as items cancelled at short notice could be re-refrigerated and re-issued before the expiry date. The costs of the five drugs doubled because pre-filled syringes were used. A preliminary analysis showed that 20 per cent of the total number of cytotoxic injections issued were in pre-filled syringes. This was at a time when the manufacturers could not meet the demand, but as this is now being addressed, the proportion of pre-filled syringes used should rise to 40 or 50 per cent of the total, said Ms McLean.

— WORK-RELATED STRESS

Stress occurs when too few people are required to do too much work, according to Professor LENNART LEVI (Emeritus Professor of Psychosocial Medicine, Department of Health Sciences, Karolinska Institute, Stockholm, Sweden). This is bearable for a short time but when it becomes the normal pattern of work it is damaging.

The concept of stress was first introduced by the Canadian biologist Hans Selye who worked with animal models. Stress was the term he gave to the common feature ("lowest common denominator") of reactions to exposures, challenges and demands of all possible types. He also described it as wear and tear on the organism or the "revving up—stepping on the gas", said Professor Levi.

A number of work-related stressors have been identified (see Panel 1) and six critical mismatches appear to be important. They are: overload, lack of control, insufficient reward, lack of community (competing instead of collaborating), lack of fairness, and role conflicts. An example of role conflict is being asked to do a perfect job but also being asked to manage with a reduced budget. "You can do one or the other — but not both", said Professor Levi. On top of the work situation, family circumstances also play a role. Women, in particular, may face considerable demands from ageing parents, adult children and/or small children. Given that 60 to 80 per cent of hospital pharmacists in Europe are female and their average age is between 40 and 50 years, this situation is likely to be familiar to many pharmacists.

It is well recognised that good support can buffer the stress generated by high demand/low control situations. On the other hand, if individuals in this situation are isolated or exposed to bullying, the effects of stress are quickly evident. Dozens of studies have shown this to be true and it translates into increased physical and mental morbidity. The good news, said Prof Levi, is that these situations are amenable to change — because they are man-made in the first place. "Why should we not create conditions of support in our workplaces?" he asked.

Another way to conceptualise the situation is using the effort-reward model. In essence, this says that a person may invest a lot of effort in a task or job either because they are "overinvolved" ("believe they are Albert Schweizer or Florence Nightingale") or because their employer makes high demands. If this effort is not balanced by a suitable reward, be it salary, recognition or appreciation, then the individual becomes frustrated, stressed and eventually suffers ill health.

Much of this is rooted in our ancient biological design, said Professor Levi. We are constructed almost identically to Nean-

derthal man, he explained. When faced with life-threatening situations, stress is the only way to prepare for them biologically. Signals from the cerebral cortex evoke neural, hormonal and immune responses at lower levels in the brain. The combined effects prepare the organism for fight or flight — the heart rate increases, muscle blood flow is increased, adrenaline is released from the adrenal medulla promoting glycogenolysis in the liver and muscles, and noradrenaline stimulates the release of free fatty acids from the fat stores. The early men who could react in this way survived, while those who could not, disappeared forever. Modern man still has the same biological make-up as those early survivors.

Three European surveys, involving a total of 21,000 interviewees, have asked about features that characterise everyday work. The results have shown a progressive increase in the numbers of people who say they are working at high speed and/or working to tight deadlines. By 2000, the proportions were 56 per cent and 60 per cent respectively. “If this is your situation,

you are in trouble”, said Professor Levi. The likely outcomes include backache, stress, muscular pains in the neck and shoulders and occupational injuries. If the situation continues then performance deteriorates and the individual approaches breaking point. It is important to realise that everyone has a breaking point, he warned.

Stress does not affect everyone in quite the same way because of the protective effects of coping. Coping is best exemplified by the ancient prayer of St Francis of Assisi; “God grant me courage to change the things I can, serenity to accept the things I cannot change and wisdom to know the difference.” Those who are able to differentiate between things in this way are generally good at coping, said Professor Levi. Another aspect of coping is social support and this comes in many guises (see Table 1).

In 2001, the World Health Organization (WHO) annual report said, “Mental health problems and stress-related disorders are the biggest overall cause of early death in Europe.” This is not only a matter of health, it also has grave economic implications. The



Lennart Levi: We need to humanise the human environment

cost of mental health problems in the 15 EU member states is now, on average, 3 to 4 per cent of the gross national products, which is equivalent to €265bn (£159) annually (at 1998 prices).

“What a waste it is not to do something about this!” said Professor Levi. This is one of reasons why he and his wife had been invited by the European Commission to prepare a report entitled, “Guidance on work-related stress: spice of life or kiss of death?”

Recently, a communication from the Commission of the European Community (CEC) had invited major companies to publish “the triple bottom line” encompassing economic, environmental and social criteria, and not just one of these. This followed the recognition that the most desirable goal was a balance between economic prosperity, environmental quality and social capital. The Swedish company, Volvo, had already taken an interest in the prevention of occupational stress and burn-out. In their scheme both employer and employees had to take some responsibility for stress prevention. Examples are shown in Table 2.

The aim of this type of programme is to avoid burn-out, with its hallmark symptoms of exhaustion, cynicism and indifference, and to maintain the workforce in a state of engagement, characterised by energy, involvement and efficiency, said Professor Levi. The present situation can be likened to trying to force feet into narrow, pointed shoes, he suggested. It was painful, and eventually it did lasting damage to the feet. “We need to change the shoes in all human settings — humanise the human environment”, he concluded.

REFERENCES

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Panel 1: Work-related stressors

- 1 Overload/underload/wrong job (eg, tasks for which operator is not trained)
- 1 Insufficient time for good performance (task acceptable)
- 1 Discrepancy between responsibility and rights (eg, being restricted in the decisions that can be made but blamed for incorrect decisions)
- 1 Unclear instructions and role
- 1 Unclear goals
- 1 Lack of support from fellow workers and management
- 1 Lack of appreciation or reward
- 1 Lack of influence or decision latitude
- 1 Exposure to violence or the threat of violence
- 1 Discrimination
- 1 Bad physical work (eg, handling cytotoxics without adequate protection)
- 1 Under-utilisation of capacity and skills leading to frustration
- 1 Mistakes have high costs or put other people’s health or lives at risk
- 1 Risk of losing one’s job (eg, through restructuring)

Table 1: Social support

Element of social support	Example
Esteem support	Telling each other of esteem; saying thank you and repeating it
Appraisal support	Encouragement
Belonging support	Carrying each other’s burdens; caring about each other
Tangible support	Money; information

Table 2: Joint approach to stress prevention

Management responsibility	Employee responsibility
Deglorify “overemployment syndrome” where the culture of working long hours is seen to be of merit	Establish a balance in work/family/leisure
Monitor overtime	Leave work at the end of the normal working day
Provide time for recuperation	Relax through non-work activities