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Safety and risk in practice

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1. Drug related hospital admissions: more attention is needed for interventions with patients

Hallas et al. from the Department of Clinical Pharmacology at the University of Odense (Denmark) investigated drug related hospital admissions (DRH) in sub-specialities of internal medicine. I have discussed earlier in "Safety & Risk in Practice" an intervention study by the Odense DRH survey group [1]. Eight publications on this issue, complemented by a comprehensive literature review on DRHs and a general discussion of the management of this problem have now been compiled in a thesis by Dr. Jesper Hallas [2]. In 1990 Hallas established the Odense Pharmacoepidemilogical Database (OPED), by means of which figures for drug use in Funen County can be linked with person-identifiable data on morbidity.

The purpose of the thesis was to throw light on various aspects of the problem of DRH: their prevalence in different patient categories, the quantitatively most important DRHs, the magnitude of the problem in relation to drug utilization and demography, effective interventions, and the future monitoring of DRHs as a part of post-marketing surveillance. The scope of the DRH program included adverse drug reactions, intentional self-poisoning, non-compliance, inadequate dosage and interactions. The survey was carried out in six departments of internal medicine at the Odense University Hospital in 1988–1989 and included data on 1999 admissions. The medical reports were reviewed prospectively. Standardised criteria were used for the assessment of causality as regards adverse reactions of drugs (ADR) and dose-related therapeutic failures (DTF). A mean 8.4% of all admissions met the criteria for a definite, probable or possible causal relation with ADRs (5.8% definite or probable ADRs). Another 3% of the admissions were related to DTFs (2.2% definite or probable). The crude incidence of DRH was 404/100,000 inhabitants/year. The incidence increased strongly with age. On average, each of the 124 general practitioners in Funen County encountered 6.7 DRHs every year, and they were directly involved in nearly 50% of these. The incidence of drug-specific ADR's was, however, generally small as compared to the drug sales figures (10–100/1,000,000 DDDs sold). Hallas et al. found that 47% of the DRHs were definitely or possibly avoidable. Although general practitioners were more often involved in avoidable DRHs than were other doctors, one must take into account the fact that in Denmark 72% of all medication is prescribed by GPs. The share of the Danish GPs in avoidable DRHs was in fact in relative terms lower than that of other doctors. Diuretics and anti-asthmatics were the drugs most frequently involved with DRHs.

The OPED registry was validated by a cohort study on the association of non-steroidal anti-inflammatory drugs (NSAID) and admission for upper gastrointestinal bleeding. Over a period of 19 months 31,503 NSAID-users (2.5 million DDDs) were studied. The investigation showed that the

standardised incidence of bleeding in particular was higher during the first month of treatment with NSAID; patients over 75 years of age and patients with previous peptic ulcer were more at risk.

Hallas et al. also carried out an intervention program for general practitioners with the purpose of reducing the incidence of avoidable DRHs. As reported earlier there was no statistically significant decrease in the rate of DRHs, but there was indeed a significant decrease in definite or possible avoidable DRHs [1]. Hallas considered that more attention should be paid to interventions performed with patients. He found that an important element in the DRH problem was the inappropriate use of over-the-counter drugs (usually salicylates).

The leitmotif of this thesis was a well-known citation of Oliver Wendell Homes (1864), even at that time very conscious of environmental problems: "If the whole materia medica, as used now, could be sunk to the bottom of the sea, it would be all the better for mankind, and all the worse for the fishes". The message provoided by Jesper Hallas is, however, not a negative one: nearly 50% of DRHs are definitely or possibly avoidable; it is a challenge to decrease them by means of effective intervention programs with doctors and patients. New computerized methods like record-linkage of databanks are important tools for post-marketing surveillance, controlling the incidence of DRH and identifying objects for interventions, as well as for monitoring the effects of this work.

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2. 'Early' genetic amniocentesis is associated with a higher fetal loss rate

Cytogenetic investigation of amniotic fluid cell cultures obtained by amniocentesis is an accurate method for the early detection of genetic abnormities in pregnancies at risk (e.g., those in women aged over 37 years). Pregnant women at risk, their family and their doctors will thereby know as early as possible the karyotype result of the cytogenetic investigation. Amniocentesis is commonly performed between the 16–19 weeks of gestation. In several centres, however, amniocentesis has been performed earlier: between the 11th and 14th weeks of gestation. The cytogenetic results of amniocentesis in the first trimester prove to be as accurate as those obtained in the second trimester. On the other hand, there have been reports of a higher complication rate following "early" amniocentesis.

Cynthia Brumfield et al. (University of Alabama, Birmingham, USA) compared the pregnancy complications following 'early' and 'late' genetic amniocentesis [1]. They studied the clinical outcome of 314 pregnant women with an amniocentesis at 11–14 weeks, compared with a control group of 628 women with an amniocentesis at the 16–19 week of gestation. All genetic amniocenteses during the study were performed by one of three maternal-fetal medicine physicians, who were highly experienced in targeted sonography and the technique of amniocentesis. Both early and late amniocentesis groups were matched for age, race, indication for genetic amniocentesis and the number of prior spontaneous abortions. The mean age of the pregnant women was 38 years. Women who had an 'early' genetic amniocentesis were found to be significantly more likely to have post-procedure amniotic fluid leakage (2.9% vs. 0.2%), post-procedure vaginal bleeding (1.9% vs. 0.2%) and fetal

loss within 30 days of the amniocentesis (2.2% vs. 0.2%) than women undergoing a 'late' amniocentesis. Four of seven women in the 'early' group who had a post-procedure fetal loss had also a post-procedure complication (fluid leakage, bleeding or infection). No differences were noted in the number of preterm deliveries, later fetal death, neonatal death and growth disturbances.

The advantage of acquiring early knowledge of the karyotype result is thus counterbalanced by a tenfold higher risk of complications and fetal loss. Brumfield et al. could not determine whether the increased fetal loss following 'early' amniocentesis is due to the procedure itself or is related to the gestational age.

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3. Traffic accidents and iatrogenic aspects

In 1994 in Switzerland 679 people lost their life and about 30,000 became injured in traffic accidents. Dr. Beer (Inselspital, Bern) and Dr. Seeger (Institut für Rechtsmedizin, Universität Zürich) estimated that about 50% of the fatalities and injuries could be avoided if medical screening and control policies were be carried out more consistently [1]. A proportion of the preventable incidents had iatrogenic aspects, connected with medical incapacity to drive. In 20% of the fatalities alcohol, drugs or combinations of the two were the cause of the accident. They found indications that the sleep apnoea syndrome was another important but often unrecognized cause of accidents. An estimated 25–30% of the traffic accidents were caused by drivers falling asleep while driving. Other commonly unrecognized medical risks for traffic accidents included cardiovascular disease, epilepsy, early Alzheimer's disease, diabetes mellitus, vision problems and psychiatric illness. Sometimes it turned out to be difficult for a physician to arrive at an objective judgement as to the driving capacities of patients. Beer and Seeger found that too little attention is devoted to drugs that can influence driving capacity.

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4. Preparation and administration of antineoplastic agents: how can one protect health care workers

Carcinogenic, mutagenic and teratogenic properties are attributed to exposure to antineoplastic agents. Hospital workers involved with the preparation and the administration of antineoplastic agents have an increased risk of developing health problems. Nurses exposed in their work to cytostatic drugs have a higher risk of spontaneous abortions and of giving birth to children with congenital defects [1,2]. Nurses working at oncology departments were found to have a calculated five-fold risk

of developing cancer in the course of a 40-year working life [3]. Genotoxic carcinogens such as cyclophosphamide and ifosfamide interact with DNA in cancer cells, but also in normal cells. Even limited levels of exposure involve a risks to health: for these agents no 'no-risk level' exists.

Despite safety measures hospital workers can easily become exposed to small amounts of these drugs during their work. Researchers at the Catholic University of Nijmegen (The Netherlands) developed methods to quantify small amounts of the antineoplastic agents cyclophosphamide and ifosfamide in urine and in the work environment [4]. The methods were validated in three hospitals. Cyclophosphamide was detected in personal and stationary air samples and in wipe samples collected in the pharmacies, as well as in several medicals and ambulatory wards where antineoplastic treatment was administered. It was also detected on gloves used for preparation and for the cleaning of laminar-downflow hoods. It appeared also that latex gloves were permeable for cyclophosphamide (!). Cyclophosphamide and ifosfamide were detected in urine samples of pharmacy, staff and of nurses involved in the preparation and the administration of these drugs. However, it was also detected in urine samples from other hospital workers who were not directly involved. Inter-individual variation of the concentrations of the unmetabolised drugs in the urine samples could not be explained merely by different levels of inhalation of polluted air at the workplace, as assessed by personal air samples. Paul Sessink et al. suggested that exposure routes were involved in contamination; the drugs might well enter via the skin [5]. The results of the study by Dutch researchers demonstrate that safety procedures around the preparation and administration of antineoplastic agents must be reassessed and improved. Biological monitoring is a useful method for detecting low levels of contamination by antineoplastic agents.

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5. A risk management program based on operational design for the preparation of antineoplastic drugs in a hospital pharmacy

Preparation of drugs and drug mixtures in the pharmacy is part of the medication process in hospitals. No valid studies, however, appear to be available of error-preventing methods in the preparation circuit, which involved numerous steps. The relevant steps are usually performed by nurses or pharmacy assistants. Errors can occur in all steps of the process. To begin with, the medical order or prescription has to be translated into a work paper (patient's name, department, antineoplastic drug, dose and administration time, route and date). Calculations have to be made for the preparation

of the drug; the preparation process has to be performed in a strictly regulated manner; labels and batches numbers have to be preared and attached to the vials, and arrangement and storage has to be carried out meticulously. Final checking is the task of the hospital pharmacist: it is her who will compare the prescription with the final product, the prescription with the work paper and the work paper with the final product.

Escoms et al. developed a design for an operational audit of the preparation process in their pharmacy at the Hospital Materno-infantil Vall d'Hebron in Barcelona (Spain) [1]. They described the preparation processes in the form of a written control schedule, and identified 20 steps or parameters which were susceptible to error ("error opportunities"). During a year 4,734 preparations were carried out, representing 94,680 error opportunities. In all 314 errors were detected. The most frequent were those involving the identification label: faults related variously to the expiry date (15%), storage conditions (14%) type of diluent used (14%) and failure to register the commercial product batch used in the preparation of the individual mixture (13%). In 11.5% of the errors the pharmacy was obliged to reject the mixture. During the study the percentage of errors per parameter decreased from 0.74% in the first month to 0.26% in the last month. This decrease was explained by the investigators by the fact that the person responsible for the error was notified after inspection by the pharmacist. The important idea behind this quality control system is that the whole operational process be strictly defined in advance. Operational audit is one of the main techniques to ensure the prevention of errors.

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6. Again and again: all doctors are fallible

In the last decade doctors have become more conscious that fallibility is a matter of discussion. There is no reason to avoid this discussion. One might as well realise, however, that this topic has already been discussed on very many occasions in the history of medicine. Even Hippocrates of Kos (460–377 AC) realized in his day that errors cannot always be avoided. In his opinion it is human to make mistakes: "It takes much effort to achieve a keen intellect and seldom to err in excess or deficit, and I am full of admiration for the physician who only makes insignificant mistakes". In the sixth century in the north of India the Buddha also taught about errors and avoiding them. "Now, look you Kalamas, do not be led by reports, or tradition or hearsay. Be not led by the authority of religious texts, nor by mere logic or inference, nor by considering appearances, nor by the delight in speculative opinions, nor by seeming possibilities, nor by the idea: this is our teacher."

The possible sources of intellectual errors whih the Buddha enumerated, are the same that we can experience today. In the *British Medical Journal*, Carlo Fonseka, professor of physiology at the University of Kelaniya at Ragama (Sri Lanka) provides a very open and personal report of five cases in which he was involved and in which he himself made fatal errors [1]. Physiological, psychological and environmental factors can predispose to error. Professor Fonseka concludes that lack of knowledge or skill were not common causes of fatal errors; in each case some rules were violated ("rule based errors"). A physician may have ignored the rule not to jump to conclusions, or the rule to treat an emergency as an emergency, or he may have deployed dishonest techniques in the belief that in some case the outcome justifies the means.

Although all doctors are fallible, their natural reaction is to hide their errors. Yet it is unethical and unscientific to refuse to face up to the errors which one has made. Facing up to our errors is in Fonseka's view the path to medical wisdom – a conclusion advanced by Tony Smith, Deouty Editor of the *British Medical Journal*, in the first issue of the *International Journal of Risk and Safety in Medicine* in 1990. In 1983 Karl Popper and Neil McIntyre wrote in the same journal: 'Making mistakes is a part of life. It is impossible not to make them. Doctors have to learn from their mistakes, and hiding them has to be considered a mortal sin' [2].

I found it interesting to discover a publication from 1912 with the same message. Richard Cabot from Boston (USA) studied 3000 autopsies, comparing the autopsy findings with the diagnosed cause of death [3]. Cabot stated that even experienced physicians are familiar with mistakes in diagnosis. Some errors are avoidable; other errors are made again and again. The physician can learn from his own errors, but his mistakes are also instructive to his colleages. Cabot makes it plain that medical results and medical failures are related more to particular methods than to particular individuals. He considers the ratio of success to failure a mirror of the methods practised in the hospital concerned. Why do we have to discover again and again lessons already advanced so long ago?

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7. Postoperative lumbal discitis

The cause of discitis after operation for a prolapse of the nuclei pulposus is most commonly a bacterial infection in the avascular disc. How this infection develops is not known [1]. Is it a nosocomial infection or just an ordinary complication within a calculated risk? In animal models prophylactic antibiotics given one hour before the operation can effectively prevent postoperative discitis [2].

In the published literature, the incidence of postoperative discitis after lumbal surgery is reported to be 0.7–4.2%. Fouquet et al. (Trousseau Hospital, Tours, France) investigated 25 suspected cases of discitis after surgery using bacterial cultures and biopsy of the disc [3]. They found bacteriological evidence of a septic discitis in nine cases, while in another eight cases the pathohistology suggested a bacterial cause. In eight cases the cultures were negative and the pathohistology showed an avascular necrosis. Petri and Panum Jensen (Hilleröd Sygehus, Denmark) reported a 2.7% incidence of postoperative discitis in a group of 620 operated patients [4]. The diagnosis was confirmed by tomographic investigation of the lumbal spine, the clinical symptoms (pain and fever) and an increased ESR. In 14 patients (82%) with clinical discitis a bacterial infection was the probable cause and in 18% an aseptic discitis was suspected.

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8. Screening programs for colorectal cancer: the gain of early detection against the risk of complications and charging patients with unnecessary investigations

One of the main problems with cancer screening programs is to find an acceptable balance between the benefit of early detection and the undesirability of excessive investigation of the patient, possible iatrogenic complications and high costs. The ideal screening test combines a high sensitivity with a high specificity. We have to find the sick patient without encumbering healthy people with false positive findings.

Kewenter and Brevinge from Sahlgrenska University Hospital at Göteborg (Sweden) reported the results of screening for colorectal cancer among 68,306 inhabitants of Göteborg between 60 and 64 years of age [1]. All patients in the screening group received by mail three tests for tracing occult blood in the stool (Hemoccult II, Smith Kline Diagnostic). A positive finding of occult blood in the faeces was followed by investigation with a 60 cm flexible sigmoidoscope (FS) and a double-contrast barium enema (DCE). When an abnormity above the sigmoid colon was suspected coloscopy was performed. Where removal of a tumour was not possible by endoscopy a laparotomy was carried out. The authors' conclusions as to the benefit and the risks of the study are limited; the researchers did not provide data on the response of the subjects screened group.

Because of a positive Hemoccult II test, 2,108 patients had a FS and on 1,987 of them a DCE was carried out. Because of an unclean intestine 39 patients (2%) had to undergo a second FS, and the DCE was repeated to 63 (3%) patients for the same reason. A coloscopy was carried out 190 times and ultimately 104 patients had a laparotomy. Using the flexible sigmoidoscope 554 polyps were removed in 413 patients. Possible adenomas above the sigmoid colon were removed by coloscopy in 113 patients. 79 carcinomas and 13 adenomas were removed by laparotomy. Four patients who underwent laparotomy had a diverticular disease, an inflammatory bowel disease was found in two patients, one patient had an aneurysm of the aorta abdominalis and on five occasions the laparotomy was necessary to exclude pathology because of unclear findings.

No complications from DCE were reported. However, three patients undergoing FS experienced a perforation when a benign adenoma was removed (0.7%), and laparotomy followed to suture the perforation. One patient needed a temporary transversotomy. Three patients with a coloscopy had a laparotomy because of perforation or prolonged intestinal bleeding (lymphangioma). A re-laparotomy was performed five times (two patients with colitis). There was no mortality. All patients recovered. In nine of a thousand people who responded in the screening group an abnormity was found. Further investigation of these patients gave a 5% detection rate of carcinomas and 15% of benign adenomas. In the light of these results Kewenter and Brevinge estimated the risk with respect of complications and unnecessary investigations acceptable.

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9. The hazards of complementary and alternative medicine

In the western world the popularity of complementary and alternative medicines is increasing rapidly. The sales of herbal medicine have increased dramatically in recent years. Disillusioned with conventional medicine, frightened by the perceived emphasis on potentially dangerous drugs and suspicious about high-tech interventions, people are turning to complementary and alternative treatment like acupuncture, osteopathy, homeopathy and herbalism. People are prone to believe that 'natural' treatment is safe and free from side effects.

Edzard Ernst from the Centre for Complementary Health Studies at the Exeter University (UK) warns that even 'natural' medicine can cause severe side effects. In Belgium and France about 80 patients had to be dialysed after using herbal medicines. Some patients died after alternative treatment [1]. The research group at Exeter asked the 500,000 readers of *The Guardian* to report their experience with alternative treatment [2]. Most of the 386 respondents had a positive attitude to complimentary and alternative medicine; 96% declared that it had improved the quality of their life. However, 24% reported adverse effects. One in eight patients treated with acupuncture complained of aggravation of the symptoms, fatigue, pain and injuries caused by the needles.

Abbott et al. asked 972 general practitioners in Cornwall and Devon (UK) about their experiences with patients involved in alternative treatments. Of the respondents 38% reported adverse events in patients. Chiropractic therapy and osteopathy were most commonly mentioned as a cause of adverse events (three fractures, two nerve injuries and a disc protrusion). Septic arthritis after acupuncture, liver failure and anaphylaxis after herbal and homeopathic medicine were also reported.

There are two hazards of complementary and alternative medicine. Beside the potential toxicity and adverse effects, there is a risk that patients with serious diseases receive therapies that have not been adequately shown to be effective.

Despite the popularity of alternative and complementary medicine virtually no proper statistical studies have been carried out in the field. In most western countries, control on marketed herbal medicine is lacking. Everyone can start a practice in alternative treatment. Only in the United States are alternative practitioners more strictly regulated.

Ernst asked 200 German companies, which produce non-licensed "alternative" medicines about the efficacy of their products. Only four companies returned reprints of published papers. He also observed that alternative practitioners were hardly interested in setting up clinical trials.

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10. British patients want to ban surgeons with hepatitis B

In London a 77 old woman died in the summer of 1996 from hepatitis B, three months after surgery for a broken hip. It was confirmed that she had caught the nosocomial infection from a locum orthopaedic surgeon who was known to be a hepatitis B carrier. The Department of Health's advisory committee on hepatitis B had cleared the surgeon to operate, and it was found that he had operated 235 patients in the last year.

The British Patients' Association reacted sharply, demanding that surgeons with hepatitis B be banned from the operating theatre. Patients have at least the right to know that they are to be operated by an infected doctor who can transmit the virus to them. Patients further have the right to refuse operation by a doctor who carries the virus. A member of the Hepatitis B Advisory Committee noted that new guidelines have to be evaluated, but banning all carrier surgeons with low levels of infection from the operation theatre, will rule out quite a number of doctors. A spokesman of the British Medical Association commented that, like patients, doctors with hepatitis B are also entitled to confidentiality.

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