International Journal of Risk & Safety in Medicine 8 (1996) 179–185
IOS Press

Safety and risk in practice

Edited by André F. Tempelaar*

1. A lesson from Bangladesh: monitoring of drug manufacture and supply in developing countries has to improve

Dr. Mohammed Hanif of Dhaka Shishu Hospital for children reported about a tragedy with diethylene glycol contaminated paracetamol elixir, causing renal failure to more than 300 Bangladesh children. In October 1990 at Dhaka Shishu Hospital a dramatic increase of admissions of children with unexplained renal failure was noted. A causal relation with paracetamol elixir was suspected, since this drug was identified as having been taken most commonly before admission.

Although the first warnings by the doctors at Dhaka Shishu Hospital were given in November 1990, and samples of the suspected drug were submitted several times to the Bangladesh Drug Administration, it took until December 1992 before the Bangladesh government intervened by banning the sale of paracetamol elixir. The Bangladesh Drug Administration and local laboratories failed to identify ethylene glycol contamination in paracetamol elixir samples. With help, however, of the World Health Organisation and the State Laboratory Institute of Massachusetts 69 samples of paracetamol elixir from 19 different Bangladesh manufacturers could be identified as containing diethylene glycol (including samples from the stock of the pharmacy of the Dhaka Shishu Hospital).

A press conference in November 1992 where the Dhaka Shishu paediatricians presented the laboratory results at last led to intervention of the Government.

The failing monitoring system and the delay in adequate governmental action were both responsible for the largest fatal diethylene glycol poisoning ever reported. Between 1990 and early 1993 at Dhaka Shishu Hospital 67 cases were registered of children with renal failure after using diethylene glycol containing paracetamol elixir; 51 of the children died. Among them were 25 children admitted to the hospital for other diseases, but acquiring renal failure after drinking paracetamol elixir from the hospital's pharmacy. Of 273 cases admitted with unexplained renal failure, an additional 185 children died, all strongly suspected of diethylene glycol poisoning. After the banning of paracetamol elixir the number of patients admitted with unexplained renal failure dropped to one in the second half of 1993.

It remained unclear how the diethylene glycol contamination had taken place. Probably importers or distributors had replaced the commonly used solvent propylene glycol by the less expensive but toxic solvent diethylene glycol.

*Correspondence address: Het Eiland 7, 7271 BK Borculo, Netherlands.

This tragedy lays open the problems which developing countries face in dealing with implementing and maintaining monitoring drug safety systems. In countries like Bangladesh a host of small pharmaceutical manufacturers are part of the pharmaceutical infrastructure. In Bangladesh more than 100 manufacturers were licensed to produce and market paracetamol elixirs. The poorly equipped drug administrations are not able to set up an adequate monitoring and control system. Okuonghae et al. reported in 1992 a similar epidemic of diethylene glycol poisoning in Nigeria causing death of 47 children.

The Bangladesh and Nigeria epidemics are warnings for other developing countries: it can happen again.

References

[1] M. Hanif, M.R. Mobarak, A. Ronan et al., Fatal renal failure caused by diethylene glycol in paracetamol elixir: the Bangladesh epidemic, *Br. Med. J.* **311** (1995), 88–91.
[2] H.O. Okuanghae, I.S. Ighogboja, J.O. Lawson et al., Diethylene glycol poisoning in Nigerian children, *Ann. Trop. Paediatr.* **12** (1992), 235–238.

2. Low-birthweight babies and the possible risk of 'cupping'

Dr. Jane Harding, neonatologist in Auckland's National Women's Hospital (New Zealand) attributed the death of five newborn babies and severe brain damage in eight other babies with low birthweight (675–1100 g) to 'cupping', a form of physiotherapy in which the chest of the baby is tapped with a soft latex cup to clear secretions. She investigated 200 files of babies admitted at the neonatal intensive-care unit of NWH and found that the brain-damaged and dead babies had received two to three times more physiotherapy than babies who were not damaged. The 'cupping' was carried out by trained intensive-care nurses.

Although a pathophysiologic explanation is unclear, Harding suspects that head movements during physiotherapy can cause dangerous fluctuations in brain blood flow. She referred to a publication by Cross et al. (Birmingham Maternity Hospital, UK) in 1992. They described a severe brain injury in 15 preterm neonates, which was named postnatal encephaloclastic porencephaly. The characteristic pathological finding was a full-thickness cortical necrosis, probably caused by unidentified postnatal traumatic events.

The relation between the brain injury and postnatal physiotherapy is a speculative one. However, Harding also notes that the commonly used 'cupping' technique lacks a scientific base. While awaiting other studies, 'cupping' on newborn babies has been banned in the Auckland hospital.

References

[1] S. Coney, Physiotherapy technique banned in Auckland, *Lancet* **345** (1995), 510.
[2] J.H. Cross, C.J. Harrison, P.R. Preston et al., Postnatal encephaloclastic porencephaly – a new lesion?, *Arch. Dis. Child.* **67** (1992), 307–311.

3. Silicone implants and connective tissue disease (II)

The controversial hypothesis that silicone breast implants have a causal association with connective tissue disease (CTD) becomes more and more unlikely. In 'Safety and risk in practice' I referred

earlier to these doubts, referring to the literature study by Sánchez-Guerrero et al. (1994) and the small Olmsted cohort study of Gabriel et al. (1994). These studies gave no support to the CTD hypothesis (*Int. J. Risk & Safety Med.* **6** (1995), 198–199).

Another study from Harvard Medical School confirmed earlier analyses. Sánchez-Guerrero et al. published recently the results of a large 14 years follow-up cohort study (Nurses Health Study cohort). This cohort was formed in 1976. Seventy percent of all female and married nurses between 30 and 55 years of age in eleven US states were included in the cohort. In 1992 109,750 women were still participating in the study and a questionnaire with questions about breast-implant surgery, silicone, paraffin or collagen injections was returned by 89,376 women (81.4%). In total 87,501 women were included in the analysis.

A supplementary questionnaire was sent to 1,861 women who reported having received breast implants or injections with silicone, paraffin or collagen. The response to this questionnaire was 97%.

The analysis included 1,183 women with confirmed breast implants in May 1990 or earlier: 876 with silicone-gel-filled implants, 170 with saline-filled implants, 67 with double-lumen implants, 14 with polyurethane-coated implants and 56 with implants of unknown type. The mean period of follow-up after surgery was 9.9 ± 6.4 years (total 11,170 person-years).

Among 87,501 women (1,181,244 person-years) 516 patients met the criteria for CTD. Three patients with definite CTD had breast implants, of which only one had a silicone-gel-implant. Possible early, milder or atypical forms of CTD were reported by 5,087 women; 32 of them had a breast implant (21 silicone-gel-filled).

The age-adjusted relative risk of a definite CTD among women with silicone-gel-filled implants was 0.3 (95% confidence interval, 0 to 1.9) as compared with women without implants. The relative risk of self-reported signs or symptoms of CTD for women with implants was 1.5 (95% c.i., 0.3–1.6).

The conclusion is that this large cohort study again provided no evidence for a causal association between silicone breast implants and the development of CTD.

References

[1] J. Sánchez-Guerrero, G.A. Colditz, E.W. Karlson et al., Silicone breast implants and the risk of connective-tissue diseases and symptoms, *N. Eng. J. Med.* **332** (1995), 1666–1670.

4. Preventing malpractice in primary care; the first goal is learning GPs to deal with errors

There is little literature on errors in general practice and the way GPs deal with them. In the Netherlands recently three interesting studies were published about this subject.

In the Netherlands the number of disciplinary law cases against GPs has increased fivefold since 1982 reaching a total of 187 in 1993. Considering that 6,500 GPs are enlisted and more than 50 millions of doctor-patient contacts take place every year, the number of disciplinary cases is extremely low. Heineman and Hubben from the Nijmegen Catholic University analyzed 409 accepted disciplinary law cases. They found that negligence in acting as a locum tenens was the most common reason for suing (27% of cases in 1992). The reason for a disciplinary measure was often refusal to visit a patient requesting assistance. Other reasons for suing were violation of professional secrecy (10%) and malfunction of the receptionist (5%). One of the purposes of their study was to find out if sentences could improve quality. Remarkable was the finding that the case law hardly made reference to standards

and protocols developed by the Dutch Society of General Practitioners. Even the verdict sometimes conflicted with the generally accepted standards. One of the things GPs could learn from these cases was always to visit a patient requesting help unless strong arguments existed for not doing so.

Marc Conradi, a sociologist from Groningen State University questioned 17 GPs about their experience with errors and faults and their opinions to the subject. He registered 101 errors and faults among the GPs concerned. Only one GP could not remember any error, but 14 others experienced errors with fatal result or serious invalidating damage. Most of the errors (80%) were made by the GPs themselves; 20% was made by other physicians. Only one GP had experienced a disciplinary law procedure.

The Canadian sociologists Stelling and Bucher described in 1973 the difficulties physicians have with giving a definition of an error. Conradi found the same emotional blocks. Some GPs related errors only with severe somatic damage. Others only mentioned errors unforgivable from the professional point of view. Errors of judgement were seldom seen as negligence. Errors that did not cause somatic damage were similarly not classified as errors. Often errors were minimized. Psychological mechanisms like denying, projection and distancing had an important role in the way the GPs experienced errors. As regards errors there existed a conspiracy of silence. Only in exceptional cases were they discussed with patients or their families, and seldom were they the subject of discussion between colleagues.

Conradi analyzed 67 events. Errors in diagnostic procedures and missed diagnoses underlay 78% of the cases (missed diagnoses of serious cardiac disease, cancer and the acute abdomen). The direct and indirect consequences were serious with a 43% fatality rate. In one of five events the GP mentioned irritation about the patient's behaviour as an adjuvant reason for his erroneous decision.

Conradi concluded that Dutch GPs define an error as a bad outcome caused by breaching existing norms of professional behaviour. The errors were incidental and did not reflect the normal standard of primary care. Dutch GPs blame themselves seriously for a missed diagnosis, especially when the outcome is life-threatening or fatal. On the other hand, none of the GPs regarded a wrong diagnosis in a healthy person as a fault! Stelling and Bucher had stated that the norms often are established in the course of socialization among a group of professionals.

In about 2% of all contacts between GPs and patients iatrogenic damage is discussed (adverse drug reactions, iatrogenic complications). The second part of the thesis of Marc Conradi discusses his efforts to set up a monitoring system for errors and accidents aimed at prevention. He questioned another 600 GPs about their likeley cooperation with such a proposed system. Most of the GPs (response 54%) had a positive attitude to a monitoring system and as many as 89% promised to report errors, accidents and near-accidents. However, in a six months pilot project with 49 GPs, only 22 of them reported an event. There is thus a considerable difference between intention and execution.

This interesting and important thesis is recommended reading for GPs. Unfortunately it is written in Dutch with only an English summary. As a former GP I was most impressed by the description of the cases. It brought the reader very close to the reality of general practice, with the great difference in patients and work, the sudden events, the sometimes hectic way of working, the pressing responsibility and the need for taking fast decisions without the support of clinical equipment. The merit of Conradi's book is that he makes the problem of errors in general practice approachable. Errors will always be made; making errors is human, and GPs are also human beings. To become aware of this is the first step towards the prevention of *unnecessary* errors.

The GPs Van Pelt-Termeer and Van den Berg showed that it is possible to discuss errors in a small peer review group of cooperating GPs. Six GPs participating in a peer review group in Vlissingen (Neth.) reported about their experiences with monthly discussion of faults and near-accidents. The group had already experienced peer review and audit with clinical and practical problems, like the

purport of referral letters, treatment of diabetes mellitus, and the contents of the doctor's bag. The group started to discuss recent events that still bothered the participants. This created an atmosphere of trust and respect. They then started a peer review on faults and (near-) accidents. All participants report monthly their most impressive incident, that could have been prevented (the "fault of the month"). The opinion of the patient was involved in the discussion. In eight sessions 39 cases were discussed.

From the point of view of the GP 34 events were "avoidable", as were 15 events assessed from the point of view of the patient (GPs and patients agreed in ten cases). The doctor's attitude (20), communication between doctor and patient (25) and careful handling of medical data (12) were factors contributing to faults and incidents. Problems with practice organisation (11) were also discussed. Although the discussion was open and in a good atmosphere, collective distancing mechanisms were observed in the group.

References

[1] M. Conradi, *Fouten van Huisartsen* (Errors of general practitioners), Boom Press, Amsterdam/Meppel, 1995 (ISBN 90-53522158).
[2] M. Conradi, J. Schuiling, M. de Bruijn et al., Towards a model on prevention of errors in general practice, *Int. J. Risk & Safety Med.* **6** (1994), 47–56.
[3] M.E.F. Heineman and J.H. Hubben, *De huisarts in de medische tuchtrechtspraak 1982–1993* (The general practitioner and medical disciplinary law 1982–1993), Koninklijke Vermande, Lelystad, 1995 (Dutch language).
[4] A.M.M. Van Pelt-Termeer and F.A. Van den Berg, Hoe heeft het kunnen gebeuren? Beoordeling van fouten en bijna-ongelukken in een toetsgroep. (How could it happen? Reviewing faults and near-accidents in a peer review group.), *Huisarts Wet* **38** (1995), 7–9/29.
[5] J. Stelling and R. Bucher, Vocabularies of realism in professional socialization, *Soc. Sci. Med.* **7** (1973), 661–675.

5. Epidural analgesia and obstetric outcome (II)

The discussion about the benefit and risk of epidural analgesia in normal physiologic delivery is still going on. Some studies showed an association between epidural anaesthesia and changing the course of labor. In other publications these studies were being criticized for methodological shortcomings: apples were compared with pears (Safety and risk in practice, *Int. J. Risk & Safety Med.* **7** (1995), 76–77).

On January 1, 1994 Tenncare insurance, a state-funded health care insurance plan was introduced in the State of Tennessee (USA). The plan was designed to serve the uninsured and those previously served by Medicaid in Tennessee. Tenncare insurance imposed restrictions on the reimbursement of routine epidural anaesthesia in childbirth. This resulted in a sharp fall in the rate of epidural anaesthesia for childbirth after January 1, 1994.

In a small-town family practice in Bristol (Tennessee) a retrospective chart review was performed to observe the influence of the insurance measure on the outcome of childbirth. Labor and delivery records of all patients who gave birth between July 1, 1993 and June 30, 1994 were examined. In the first half year of the study 96 women gave birth vaginally and 20 had a cesarean section. In the second period (after the Tenncare restriction measure), 84 women gave birth vaginally and 19 had a cesarean section. Most of the patients were insured by Medicaid and Tenncare. The number of large-for-gestational age babies was the same in both groups, as was the ratio between primiparas and multiparas.

The number of childbirths with epidural analgesia dropped from 71% in the last six months of 1993 to 27% in the first six months of 1994. The number of sections stayed constant, but the number of forceps deliveries dropped from 14% to 1%.

The length of second-stage labor was shorter without epidural anaesthesia (45% for primiparas and 57% for multiparas).

The authors concluded that epidural anaesthesia may be deleterious to the mother and possibly to the child. But the conclusion also can be drawn that restriction of reimbursement has a better influence on medical "overcare" than do medical quality programmes.

References

[1] S. Johnson and J.A. Rosenfeld, The effect of epidural anaesthesia on the length of labor, *J. Fam. Pract.* **40** (1995), 244–247.

6. Complications and late sequelae of nasotracheal intubation

An intensive care unit of the Aarhus Kommunehospital (Denmark) investigated prospectively the early complications and late sequelae to nasotracheal intubation. During intubation and up to five days after extubation all complications and lesions of the nose, nasal cavity, ears and larynx were registered. In a follow-up after 1–2 years the surviving patients were questioned about late persisting sequelae.

The study included 379 patients with a mean intubation period of 26.3 hours; 65% were intubated longer than 48 hours and 16% longer than five days. Surgery of the heart was in 58% the reason for the intubation.

During hospitalisation 400 complications were reported to 250 (66%) patients: inflammation and ulceration of the nostrils and nasal septum (20% and 29%), bleeding of the nasal cavities (19%), fractures of the conchae (11%) and hoarseness (42%). Inflammation and ulceration were correlated with the duration of intubation.

The follow-up after 1–2 years included 281 patients: 62% of them still had complaints; 35% had complaints of the nose and nasal cavity, 24% had problems in the ears, 20% in the maxillar sinus, 32% pain in the throat and 29% still had a hoarse voice. A correlation was also found between the persisting complaints of the larynx and the duration of intubation.

Because of the high percentage of complaints and long-term sequelae dr Holdgaard recommends performing orotracheal instead of nasotracheal intubation. When longterm intubation is necessary, early tracheostomy should be considered.

References

[1] H.O. Holdgaard, J. Pedersen, B.A. Schurizek et al., Komplikationer og senfölger efter nasotrakeal intubation (Complications and persisting sequelae to nasotracheal intubation), *Ugeskr. Laeger.* **156** (1994), 7353–7357.

7. Septic complications after the use of lipid-based anaesthetics: the need for aseptic handling

Propofol (2.6-di-isopropylphenol) is an intravenously administered anaesthetic formulated in a lipid emulsion, containing no preservative to prevent bacterial growth. Lipid-based medications, however, support rapid bacterial growth at room temperature. Veber et al. from Bichat-Claude Bernard Hospital in Paris (France) reported in 1994 a severe outbreak of Klebsiella pneumonia sepsis in four patients

who had undergone clean surgical procedures on the same day in the same operating room. Three of the patients had been admitted to intensive care. A vial with propofol, contaminated after opening was found to be the cause of the nosocomial septic infection. The open vial had been used for several patients over a period of more than 12 hours.

Between 1990 and 1993 the US Centers for Disease Control and Prevention (CDCP) investigated unusual outbreaks of bloodstream infections after surgical procedures in seven hospitals. With epidemiologic techniques Bennett et al. found a relation between the use of the anaesthetic propofol and septic complications in 49 patients. In all cases propofol was contaminated after opening of the vial. The contamination was due variously to mishandling (insufficient disinfection, re-use of infusion pumplines in different patients, etc.) and disregarding the advice of the manufacturer (a single-use product to be discarded within 6 hours after opening of the vial).

Up to May 1994 155 reports were received at the CDCP of nosocomial septic infections probably caused by contaminated vials with propofol. Bennett et al. found at least 38 clusters of septic complications after administration of propofol.

Because of the increasing use of lipid-based anaesthetics the CDCP warned of the risks of using this agent in a careless way. Use of a vial or ampoule for a single patient and aseptic techniques are obligatory for administration of anaesthetics like propofol.

References

[1] S.N. Bennett, M.M. McNeil, L.A. Bland et al., Postoperative infections traced to contamination of an intravenous anaesthetic, propofol, *N. Eng. J. Med.* **333** (1995), 147–154.
[2] R.L. Nichols and J.W. Smith, Bacterial contamination of an anaesthetic agent, *N. Eng. J. Med.* **333** (1995), 184–185.
[3] B. Veber, B. Gachot, J.P. Bedos et al., Severe sepsis after intravenous injection of contaminated propofol, *Anesthesiology* **80** (1994), 712–713.

8. Immunisation in primary care centres: don't forget the freezer's temperature

Immunisation is a disease-prevention goal in WHO's "Health for All 2000" programme. In many countries primary care centres are involved with immunisation programmes. The vaccines to be used are often stored in physicians' offices.

A weak link in the prevention chain proves to be the storage of vaccines. Most vaccines need to be stored under optimal temperature conditions. Too high or too low a temperature can lead to decrease or loss of potency of the vaccine. Manufacturers recommend storing most vaccines between 2–8°C.

In 27 physicians' offices in Grand Junction (Colorado, USA) the storage conditions of the vaccines were investigated. The results were disappointing. In only two offices were the vaccines stored under good conditions. In some offices (8) cold chain monitors were present, but correlation with appropriate monitoring and vaccine storage was incomplete. In other offices (9) thermometers were not correlated with storage temperatures. In 14 offices the officials did not even know the optimal storage temperature.

To attain prevention goals in immunisation programmes, optimal storage thus needs due attention.

References

[1] E. Woodyard, L. Woodyard and W.A. Alto, Vaccine storage in the physician's office: a community study, *J. Am. Board Fam. Pract.* **8** (1995), 91–94.