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EDITORIAL

Pharmacovigilance is becoming an important topic and its scope is widening. Exchange of information among regulators, professionals working in pharmacovigilance centres, industry and communication of this information to consumers and the media are being recognized as some of its essential components. This is highlighted in an article found in this issue on the workshop which took place in Hong Kong immediately prior to the tenth International Conference of Drug Regulatory Authorities. A comprehensive study on adverse drug reactions to metamizole in Sweden has recently been published. We have abstracted this article in the section Drugs of Current Interest. It shows definitively that metamizole does carry a high risk of agranulocytosis in Swedish patients.

The third informal consultation meeting on Harmonizing Safety Monitoring was held in WHO, Geneva in early September. A major topic of discussion this year was the linking of pharmacovigilance with public health programmes including malaria, schistosomiasis and HIV/AIDS and ways in which pharmacovigilance could be integrated into these programmes to promote the safe and rational use of medicines.

A WHO-UMC training course on pharmacovigilance will be held in Canberra, Australia at the beginning of November. It is the first time such a course has been held outside Sweden and we are grateful to the Therapeutic Goods Administration (TGA) in Australia for hosting this. We hope to see a large number of you at this course.

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ARISTOLOCHIC ACID

Warnings on more products containing Aristolochic acid

Canada. Health Canada is advising Canadians not to consume Longdan or Lung Tan Xi Gan products since they may contain herbs with aristolochic acid. Aristolochic acid is considered carcinogenic and has been shown to cause mutations in human cells and end-stage kidney failure. Health Canada is working with the manufacturers, distributors and importers to recall these products in Canada. A customs alert has also been issued, to prevent the importation of these products into Canada. Health Canada first issued a warning on aristolochic acid in November 1999 that this ingredient posed a Class I Health Hazard with a potential to cause serious health effects or death.

Readers are referred to previous issues of the WHO Pharmaceuticals Newsletter (Nos. 2&3, 2001; Issue No. 1, 2002; Issue No. 2, 2002) for earlier reports on safety and regulatory measures on aristolochic acid-containing products in other countries.

Reference:
Health Canada Warnings/ Advisories, 16 May 2002. Available from URL: http://www.hc-sc.gc.ca

ARTHRIN, OSPORO, POENA AND OTHERS

Presence of undeclared prescription drugs poses health threat

Canada. Health Canada is warning Canadians not to use seven herbal products, namely, Arthrin, Osporo, Poena, Neutralis, Oa Plus, Ra Spes and Hepastat, manufactured by Botanic Lab in the United States since they contain undeclared prescription drugs that could cause serious adverse effects if taken without medical supervision. The prescription drugs include indomethacin (a non-steroidal anti-inflammatory drug), diethylstilbestrol (a nonsteroidal estrogen) and alprazolam (an anti-anxiety drug). Consumers are advised to use only those products with an eight-digit Drug Identification Number (DIN) on the label. The DIN indicates that Health Canada has assessed the product for safety, effectiveness and quality. Those who have been using the affected products should discontinue their use and should consult their health care practitioners. Health Canada is working with importers to recall the remaining affected products from the market.

Reference:
Health Canada Warnings/ Advisories, 19 Jun 2002. Available from URL: http://www.hc-sc.gc.ca

ASPIRIN

Restrictions on use in children extended to teenagers

UK. Reports of Reye's syndrome associated with aspirin use in children ≥ 12 years of age have prompted the UK Medicines Control Agency's Committee on Safety of Medicines (CSM) to revise the prescribing advice for aspirin. The CSM now advises that aspirin use should be avoided in children aged ≤ 15 years of age, if feverish. The recommendation that aspirin should not be given to children <12 years of age, unless medically indicated, remains unchanged. Although the incidence of Reye's syndrome has declined markedly since 1986, when the CSM advised against aspirin use in children aged < 12 years, sporadic cases continue to be reported. Since 1986, the CSM has received 17 reports of Reye's syndrome associated with aspirin use; 7 cases were in children <12 years of age, and 10 were in persons aged ≥ 12 years. There were an additional 5 reported cases in persons aged ≥ 12 years, in which there was no evidence of aspirin use. The agency says that all possible cases of Reye's syndrome, regardless of the patient's age or exposure to aspirin, should be reported to the CSM through the Yellow Card Scheme.

Reports in WHO-file:
Reye´s syndrome 26

Reference:
Current Problems in Pharmacovigilance 28: 4, Apr 2002.

BACLOFEN

Life threatening sequelae and/or death with abrupt withdrawal of intrathecal injections

USA, Canada. Novartis Pharmaceuticals Corporation, manufacturer of baclofen intrathecal injection, indicated in the management of severe spasticity of cerebral and spinal origin, has updated the product prescribing information due to rare reports of life-threatening sequelae or death following abrupt withdrawal of the intrathecal therapy. A boxed warning has been added to indicate that abrupt withdrawal could, regardless of cause, result in sequelae including high fever, altered mental status, exaggerated rebound spasticity and muscle rigidity that, in rare cases, could advance to rhabdomyolysis and, multiple organ-system failure and death. Additional details are included in the 'Warnings' subsection entitled 'Withdrawal'. It is noted that, in the first 9 years of marketing, there have been 27 cases of withdrawal-related events temporally related to abrupt discontinuation of baclofen therapy, including 6 fatalities. In most cases, symptoms of withdrawal, which could occur in any patient, appeared within hours to a few days of discontinuation of intrathecal baclofen. Early symptoms may include the

return of baseline spasticity, pruritus, hypotension, and paraesthesias, while more advanced symptoms may resemble autonomic dysreflexia, sepsis, malignant hyperthermia or neuroleptic malignant syndrome. Prescribers are advised that rapid diagnosis and treatment are required to prevent life-threatening central nervous system and systemic effects of baclofen withdrawal; the recommended treatment for intrathecal baclofen withdrawal is restoration of intrathecal baclofen at the same dosage received before interruption of therapy.

Reference:

1. *'Dear Healthcare Provider' letter from Medtronic, USA, Apr 2002. Available from URL: http://www.fda.gov*
2. *'Dear Healthcare Provider' letter from Novartis Pharmaceuticals Canada Inc, Jul 2002. Available from URL: http://www.hc-sc.gc.ca*

BEJAI BOWYANTAN

Risk of toxicity in children due to presence of Borneol

Canada. Health Canada is warning Canadians not to use Bejai Bowyantan in young children and infants since the product contains borneolum syntheticum, a substance known to be extremely toxic, particularly in children. Bejai Bowyantan is a Chinese medicine used to treat babies with flu, fever, stomach aches, diarrhoea, night crying and inability to sleep. Although no adverse reactions to this product have been reported so far, Health Canada is issuing this advise as a precautionary measure and is in the process of identifying all importers of the product to facilitate its rapid removal from the market. A customs alert will prevent the further importation of the product into Canada.

Reference:

Health Canada Warnings/ Advisories, 14 Jun 2002. Available from URL: http://www.hc-sc.gc.ca

CELECOXIB

CLASS findings added to product label

Canada, USA. Changes to the labelling for celecoxib (Celebrex) have been announced in Canada and the US and are based on the results of the Celecoxib Long-term Arthritis Safety Study (CLASS). Celecoxib is a non-steroidal anti-inflammatory drug (NSAID) approved for use in the acute and chronic treatment of osteoarthritis (OA) and rheumatoid arthritis (RA) in adults. Health Canada is advising Canadians that, in the CLASS results :

- There were no differences in the risk of ulcer complications (gastrointestinal bleeding, perforation and obstruction) among the 3 groups of arthritis patients treated with celecoxib (Celebrex, 400 mg twice daily; 4-fold and 2-fold greater than the daily recommended OA and RA doses respectively), diclofenac and ibuprofen (75 mg twice daily and 800 mg thrice daily, respectively; common therapeutic doses for OA and RA).
- In the indicated doses, the risk of ulcer complications and symptomatic ulcers (ulcers with abdominal pain, dyspepsia, nausea or vomiting) was lower for celecocib (Celebrex) than for ibuprofen, but not different from diclofenac.
- The risk of ulcer complications in patients taking celecoxib (Celebrex) and low dose aspirin was four times that of patients taking celecoxib (Celebrex) alone.

The US FDA has advised that the following safety data from CLASS be included into the product label

- The overall safety of celecoxib used (400 mg twice a day) at twice the highest approved dose for rheumatoid arthritis was similar to commonly used doses of diclofenac and ibuprofen
- The high doses of celecoxib used (400 mg twice a day) were not associated with an increased rate of serious cardiovascular events compared with diclofenac and ibuprofen
- Patients receiving celecoxib had fewer clinically relevant reductions in haemoglobin compared with patients receiving diclofenac or ibuprofen
- Patients receiving both low-dose aspirin and celecoxib had a higher rate of gastrointestinal (GI) events than those receiving celecoxib alone.

The new labelling will also include information regarding the risk of serious GI and renal effects in elderly patients.

Reference:

1. *Gastrointestinal toxicity with celecoxib vs non-steroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomised controlled trial. Celecoxib long-term arthritis safety study. JAMA 284(10): 1247-55, 13 Sep 2000.*
2. *Health Canada Warnings/Advisories, 23 May 2002. Available from URL: http://www.hc-sc.gc.ca*
3. *FDA Talk Paper, 7 Jun 2002. Available from URL: http://www.fda.gov*

EPOETIN-ALFA

Important safety update

Canada. Janssen-Ortho Inc, in association with Health Canada has issued a 'Dear Health Professional' letter about the addition of a boxed section in the product monograph of epoetin-alfa (Eprex). The addition recommends that epoetin-alfa should be administered by the intravenous (IV) route rather

than the subcutaneous (SC) route in patients with chronic renal failure. This advice is based on the fact that most of the worldwide reports of pure red cell aplasia (PRCA) in patients treated with epoetin-alfa have been associated with SC administration of epoetin-alfa. Furthermore, antibodies to erythropoetin were detected in 63 of the 79 cases of PRCA studied. Since scientific literature suggests that all exogenous proteins have the potential to elicit an immune response, particularly when administered by the SC route, the present advise to adopt the IV route of administration aims to reduce the immune response to epoetin-alfa and thereby reduce the incidence of PRCA. Janssen-Ortho will continue to investigate the multiple aspects contributing to antibody formation and PRCA in patients receiving epoetin-alfa.

Reference:
'Dear Health Professional' letter from Janssen-Ortho Inc, 25 Jun 2002. Available from URL: http://www.hc-sc.gc.ca

GLITAZONES

FDA strengthens labelling for cardiovascular risks

USA. The US FDA has issued a safety alert advising healthcare professionals of changes to the labelling for pioglitazone (Actos) and rosiglitazone (Avandia). The changes more clearly define the cardiovascular risks associated with the use of thiazolidinediones as monotherapy and in combination with other anti-diabetic agents, particularly insulin. The summary from the FDA alerts physicians and patients to the possibility of fluid retention when either pioglitazone or rosiglitazone are used alone or in combination with insulin and warns that fluid retention may lead to, or exacerbate, congestive heart failure (CHF). It notes that cases of CHF have been reported in association with both agents, post-marketing. Included in the labelling for each drug is information from clinical trials in which the use of pioglitazone or rosiglitazone in combination with insulin was associated with an increased incidence of CHF compared with insulin therapy alone. The labelling for pioglitazone and rosiglitazone advises that patients receiving either agent should be observed for signs and symptoms of heart failure and that, if any deterioration in cardiac function occurs, the drug should be discontinued. Patients are advised to report possible symptoms of heart failure to their physician immediately. Neither drug is recommended for use in patients with New York Heart Association Class III and IV cardiac status.

Reports in WHO-file:
Pioglitazone; Cardiac failure 171, cardiac failure left 5. Rosiglitazone; Cardiac failure 281, cardiac failure left 19, cardiac failure right 1

Reference:
Actos-Avandia Safety Information Summary from US FDA, 26 Apr 2002.
Available from URL: http://www.fda.gov/medwatch/SAFETY/2002/summary-actos-avandia.PDF

HORMONE REPLACEMENT THERAPY (HRT)

Product information updated

UK. The UK Medicines Control Agency has issued new product information for hormone replacement therapy (HRT), following a review of the risks of cardiovascular disease and cancer associated with HRT by the agency's Committee on Safety of Medicines. To date, no proven benefit or harm has been shown for the use of HRT with respect to cardiovascular disease. Randomised controlled trials showed slightly increased rates of coronary heart disease in the first 1–2 years of HRT use, with a possible decrease in later years. The agency advises that HRT is not indicated for the prevention of cardiovascular disease. Recent randomised controlled trials have confirmed an increased risk of venous thromboembolism (VTE) in women using HRT, and suggest that the risk may be higher than shown in observational studies. The risk of VTE with HRT is higher in older women and in women with other risk factors for VTE. The summary of product characteristics now states that previous estimates of the increased risk of developing breast cancer associated with HRT are numerically uncertain. In addition, new evidence suggests that the increased risk of breast cancer with HRT applies to both estrogen-only therapy and estrogen combined with a progestogen. The addition of a progestogen is not protective and may increase the risk of developing breast cancer. Recent evidence also suggests that the increased risk of endometrial cancer associated with long-term estrogen-only HRT use, compared with non-use, also applies to combined estrogen/progestogen therapy. However, the addition of a progestogen does appear to reduce the risk. Observational studies suggest that, after 10 years of use, there are about 20 extra cases of endometrial cancer per 1000 women treated with combined HRT compared with approximately 42 extra cases of endometrial cancer with estrogen alone. Combined HRT is recommended for women with residual endometriosis, as unopposed estrogen may stimulate residual foci, even after hysterectomy.

Reference:
New product information for hormone replacement therapy. Current Problems in Pharmacovigilance 28: 1, Apr 2002.

IRINOTECAN

Labelling updated

USA. Pharmacia, in conjunction with the US FDA, has issued a 'Dear Healthcare Professional'

letter advising prescribers of recent changes to the prescribing information for irinotecan (Camptosar). Irinotecan is indicated as a component for the first-line treatment of metastatic colorectal cancer in combination with 5-fluorouracil (5-FU) and leucovorin and for the treatment of metastatic colorectal cancer that has recurred or progressed following initial 5-FU based treatment.

The prescribing information has been revised to identify patients at higher risk of severe toxicity, to clarify dose modification guidelines and to augment information about the management of treatment-related toxicities. Principal changes reflect that Warnings and Precautions sections of the package insert now state that:

- patients with diarrhoea should be carefully monitored and treated with fluids and electrolytes if they become dehydrated, or with antibacterials if they develop ileus, fever or severe neutropenia
- subsequent courses of antineoplastic therapy should be delayed in patients who develop diarrhoea after the first cycle of treatment until pre-treatment bowel function has resumed for ≥ 24 hours. If grade 2, 3 or 4 late diarrhoea develops, subsequent doses of irinotecan should be reduced.

The FDA has agreed with its

ISOTRETINOIN

Reports of central nervous system disorders

Norway. Reports of central nervous system disorders associated with isotretinoin (Roaccutan) have been received by the Norwegian Medical Products Agency (MPA) and, changes to the product labelling are to be made accordingly. In Norway, isotretinoin is only available through a special license for compassionate use and requires the prescribing physician to take special responsibility for the patient. Included among the reports of psychiatric adverse events the agency has received are two reports of suicidal thoughts and suicide. Although the relationship between isotretinoin and suicide is unclear, the MPA has requested that the manufacturer of 'Roaccutan' informs dermatologists that a positive relationship cannot be excluded. In addition, the MPA states that the prescribing physician must evaluate the mental health of the patient before the agent is used and, monitor the patient for depressive symptoms throughout therapy. It has also requested that a warning regarding psychiatric adverse reactions be included in information given to the patient.

Reports in WHO-file:
Depression 1389, depression aggravated 89, depression psychotic 35, suicide attempt 509

death of a woman in Australia who used a medicine containing kava. Sponsors and retailers have been asked to remove all products containing kava from the market place immediately. Consumers have been advised to safely discard kava-containing products in their possession. In addition, the TGA will undertake further evaluation of the use of kava for any additional regulatory action.

As of 17th June the Federal Institute of Germany withdrew all kava-kava and kavaine containing products from the German market due to hepatotoxic risks and insufficiently proven efficacy of these products. The regulation included homeopathic products with dilutions up to D4. The German regulation applies to all kava-containing pharmaceutical formulations.

Following a provisional opinion from the UK Committee on Safety of Medicines (CSM), the Medicines Control Agency (MCA) is to consult on a proposal to prohibit the sale, supply or importation of unlicensed medicinal products containing kava in the UK. The CSM reviewed the issue of kava-associated liver toxicity in December 2001 following the emergence of safety concerns in Europe. At that time, stocks of kava were voluntarily withdrawn by the herbal sector while the safety concerns were under investigation. To date, the MCA is aware of 68 cases worldwide