Reports on Individual Drugs

The life-threatening risks of therapy substitution

When a pharmaceutical product is withdrawn from the market for safety reasons, it is normal to propose a replacement therapy and to give advice and instructions on substitution of a similar product. However, as recently demonstrated following the withdrawal of mibefradil (Posicor®), a change in treatment can sometimes prove to be life-threatening.

In mid-1997, mibefradil was introduced as a new nondihydropyridine calcium channel blocker for the management of hypertension and chronic stable angina. The drug was long-acting, with a half-life of between 17 and 25 hours, blocking both the T-type (transient) and the L-type (long-acting) calcium channels (1, 2). Because other available calcium channel blockers acted upon the L-type channel only, mibefradil was unique in terms of mechanism of action, although the rationale for this characteristic remains less well documented (3). As a result of this selective T-type calcium channel blocker activity, mibefradil was classified as a new category of calcium antagonist in the expectation that it would hold advantage over older calcium channel blockers.

In June 1998, following reports of serious interactions with some 25 commonly used drugs, the manufacturer voluntarily withdrew mibefradil from some 38 countries worldwide (4). Since mibefradil was not demonstrated to offer specific benefits over other drugs in the same therapeutic category, its complicated drug interaction profile was assessed to be an unreasonable risk to patients. The manufacturer urged physicians to contact patients, discontinue treatment and arrange an alternative therapy (5).

However, upon introduction of alternative therapy, some new and unexpected life-threatening reactions occurred (2). Four cases of cardiogenic shock in patients previously taking mibefradil and beta-adrenoreceptor antagonists were reported after a change to substitute dihydropyridine calcium channel blockers (nifedipine, felodipine or nisoldipine). One case resulted in death, and the other three cases required intensive care.

The long half-life of mibefradil may explain these severe reactions (2). It has been proposed that a prolonged wash-out period lasting from three days to two weeks after mibefradil discontinuation may be necessary before other hypertensives such as beta-adrenoreceptor antagonists and other calcium channel blockers can be introduced. The manufacturer has now issued amended instructions for initiating substitution therapy (see page 237).

It is often the case that postmarketing surveillance of a new drug will disclose previously unexpected adverse drug reactions or interactions. However, any subsequent withdrawal of the product and recommendations for substitution therapy also require careful and considerable reflection.

References


5. Dear Doctor letter from Roche Laboratories, 8 June 1998.

Revision of HIV treatment guidelines

When the British HIV-1 Association (BHIVA) guidelines on antiretroviral treatment of HIV-positive individuals were first published in April 1997 (1), it was already acknowledged that they would require updating on a regular basis given the rapid development of HIV therapies.
As more experience is gained and newly documented evidence becomes available, treatment regimens undergo modification. In this respect, data from two large clinical endpoint studies have recently been presented which demonstrate superior clinical benefit in the use of triple combination therapy compared to dual combination therapy in HIV-positive individuals who have either been treated with zidovudine or are treatment naive.

The revised criteria for initiation of antiretroviral therapy in HIV-infected adults, as presented in the latest BHIVA guidelines (2) are the following:

**Therapy should be initiated:**
- When the patient agrees to treatment;
- When benefit outweighs the possible risks of therapy;
- When the CD4 count is >350 cells/ml;
- When the viral load value is associated with risk of disease progression.

**Therapy should consist of:**
- **<50 000 RNA copies/ml:** two nucleoside analogues plus a non-nucleoside reverse transcriptase inhibitor or HIV protease inhibitor.
- **>50 000 RNA copies/ml:** two nucleoside analogues plus one or two HIV protease inhibitors.

**The aim of therapy in treatment-naive patients will be:**
- To reduce plasma viral load to less than 400–500 copies/ml (and preferably <50 copies/ml) by 24 weeks of therapy.
- To improve and extend the length and quality of life.

In July 1998, the International AIDS Society — USA Panel has also updated its recommendations for antiretroviral therapy in HIV infection to bring them in line with currently available information (3). The Panel reviewed clinical and basic scientific studies, information from phase III clinical trials, and clinical, virological and immunological endpoint data. It also evaluated presentations made at research conferences. The Panel concluded that, overall, these data continue to support early introduction of potent antiretroviral therapy in patients with HIV infection. The variety of combination regimens which now demonstrate potency will allow a wider choice when initiating therapy.

The Panel recognized the important contribution of plasma HIV RNA assays of increased sensitivity in monitoring the therapeutic response. However, more data are needed to determine precisely the HIV RNA levels that indicate treatment failure.

With sustained monitoring, it will be possible to evaluate the long-term implications and prolonged use of HIV regimens and determine future dosages. Adverse reactions to HIV protease inhibitors reported so far include hyperglycaemia, hyperlipidaemia, peripheral fat redistribution (lipodystrophy) and visceral fat accumulation. Thus, the optimal long-term treatment approaches to management of HIV still need to be defined.

**References**


**Levonorgestrel for emergency contraception**

The most commonly used emergency contraception until now, the Yuzpe method, was developed in the early 1980s. It is based on a modified regimen of combined oral contraceptive pills containing ethinylestradiol 100 µg plus levonorgestrel 0.5 mg or dl-norgestrel 1.0 mg, repeated 12 hours later. This regimen prevents about 75% of pregnancies that would have occurred without this treatment. However, about 50% of treated women report nausea and more than 20% vomiting. There is thus a need for a more effective and better tolerated method.

Researchers working with the UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP) confirm that the use of levonorgestrel alone for emergency contraception is more effective and produces side effects in considerably fewer users than the Yuzpe regimen (1).

Levonorgestrel is a synthetic derivative of the hormone progesterone. It is one of two active compounds present in combined oral contraceptive pills. In the regimen proposed for emergency contraception, two pills each containing 0.75 mg of levonorgestrel were administered at an interval of 12 hours. In a single WHO-supported study carried out in Hong Kong, levonorgestrel was slightly but not significantly more effective than the Yuzpe regimen in preventing pregnancy. In particular, the
proportion of women experiencing vomiting was 2.7% with levonorgestrel compared to 22.4% with the Yuzpe regimen.

A double-blind randomized trial in 21 centres worldwide was subsequently designed to compare the two regimens in women, administered within 72 hours of unprotected sexual intercourse. Among the 1998 women who took part in the double-blind randomized trial, the crude pregnancy rate was 1.1% (95% CI: 0.6–2.0) in the levonorgestrel group compared to 3.2% (95% CI: 2.2–4.5) in the Yuzpe regimen group. The proportion of pregnancies prevented compared to the expected number without treatment was 85% with the levonorgestrel regimen and 57% with the Yuzpe regimen. The efficacy of both treatments was significantly and inversely related to time since unprotected coitus (p=0.01). The sooner treatment is initiated, the better it works.

The levonorgestrel regimen was more efficacious and better tolerated than the Yuzpe regimen. Women in both groups reported the same side effects: nausea, vomiting, dizziness, fatigue, headache, breast tenderness and lower abdominal pain. However, for each of these side effects, women in the levonorgestrel group reported them less frequently (2).

Replacement of the Yuzpe method with levonorgestrel should improve the acceptability and efficacy of hormonal emergency contraception. Family planning programmes may wish to consider making a change based on these findings.

References


Cancer risk in women exposed to diethylstilbestrol in utero

Diethylstilbestrol (DES) was commonly used before 1970 for the prevention of spontaneous abortion and premature delivery. Several million pregnant women in the United States of America and Europe were exposed to DES before a strong association was reported in 1971 between use of the drug in pregnancy and the occurrence of clear cell adenocarcinoma in exposed female offspring (1).

In the mid-1970s, several cohorts of DES-exposed daughters and unexposed comparison groups were followed for the occurrence of cancer, precursor lesions and reproductive side effects. The result of DES exposure on male offspring is still unknown. Animal studies have suggested an increased risk of testicular cancer, but results in case-control studies have been inconsistent (2).

Some 30% of girls exposed in utero to DES present a cervical vaginal adenosis and concern has arisen that DES may also result in a higher risk of breast cancer (3). A study has been carried out of breast and other cancers in women exposed in utero to DES by combining the previously identified cohorts and extending the follow-up from 1978 to 1994. A total of 4536 DES-exposed daughters (68110 person years) and 1544 nonexposed women (22 599 person years) were identified. The rate ratio for breast cancer was 1.18 (95% CI: 0.56–2.49) and adjustment for known risk factors did not alter this result. Similarly, there was no increased risk for all cancers or for individual cancer sites, except for clear cell adenocarcinoma of the vagina and cervix.

Three cases of vaginal clear cell adenocarcinoma occurred among the exposed daughters, resulting in a standardized incidence ratio of 40.7 (95% CI: 13.1–126.2) in comparison with population-based incidence rates. All these cases occurred among 29 111 person years accumulated by the cohort up to 29 years of age. The authors of this study concluded that since the majority of women were currently under 50 years of age, it is still important to continue to monitor cancer risk as the cohort ages into the menopausal years.

References

Zidovudine for mother-to-child transmission of HIV

Mother-to-child transmission of HIV infection is a major factor in child health and survival. The average rate of vertical HIV transmission is around 25%, but rates differ significantly between countries. These may vary from 14% in Europe to 45% in sub-Saharan Africa. Breastfeeding may be responsible for the higher rates in developing countries.

Many antiretroviral drugs have been developed to treat HIV infection and the use of zidovudine to reduce vertical transmission is now standard practice in many countries, with a consequent reduction in perinatally acquired HIV. A clinical trial in Thailand using zidovudine twice daily from 36 weeks gestation until delivery in women who did not breastfeed showed a 51% reduction in transmission risk (1). WHO recommends the regimen used in this study for settings where practical and budgetary considerations preclude the use of zidovudine or other therapies for longer periods.

The following important issues should be considered before implementing antiretroviral therapy for prevention of vertical transmission (2):

- It is important to improve access to and quality of services and to assure adequate and functioning antenatal care. Health care workers will require additional training in the administration of anti-HIV therapies.

### Table 1. WHO recommended short course zidovudine (ZDV) regimen to reduce mother-to-child transmission – possible schedule

<table>
<thead>
<tr>
<th>Action</th>
<th>1st visit</th>
<th>2nd visit</th>
<th>3rd visit</th>
<th>4th visit</th>
<th>delivery and postnatal care</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>16 weeks</td>
<td>24–28 weeks</td>
<td>34–36 weeks</td>
<td>antenatal care</td>
<td></td>
</tr>
<tr>
<td>Screen for risk factors</td>
<td>observe,</td>
<td>Assess</td>
<td>Assess</td>
<td>Assess</td>
<td></td>
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<tr>
<td></td>
<td>score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screen and treat/HIV testing</td>
<td>anaemia, blood pressure, rapid plasma reagin HIV pretest/counsel</td>
<td>anaemia blood pressure HIV testing</td>
<td>anaemia blood pressure</td>
<td>anaemia blood pressure</td>
<td></td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>*mebendazole *iron + folate *tetanus toxoid</td>
<td>*antimalarial *iron + folate *tetanus toxoid</td>
<td>*antimalarial *iron + folate *antimalarial</td>
<td>*iron + folate</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>intensive treatment with oral zidovudine 300 mg twice a day from 36 weeks until delivery</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>300 mg every 3 h of labour-delivery</td>
<td></td>
</tr>
<tr>
<td>Individual counselling</td>
<td>where to give birth results of rapid plasma reagin inform of voluntary confidential testing</td>
<td>test results and counselling - refer to support groups/services</td>
<td>infant feeding if HIV positive, consent for ZDV therapy</td>
<td>birth plan decision on infant feeding compliance with regimen</td>
<td>support for decision on infant feeding</td>
</tr>
<tr>
<td>Inform</td>
<td>obtain clean delivery kit how to seek care</td>
<td>how to prepare for birth and plan for emergency</td>
<td>if home delivery plan steps</td>
<td>receive clean delivery kit</td>
<td>refer HIV+ mothers for care/support</td>
</tr>
<tr>
<td>Plan for follow up</td>
<td>next visit/routine * bring partner</td>
<td>next visit/routine</td>
<td>follow-up after birth, child immunization</td>
<td></td>
<td>family planning *partner counselling</td>
</tr>
</tbody>
</table>

* as necessary
• Voluntary confidential counselling and testing are the cornerstones of an HIV care service. Whenever possible, partners should also be counselled and offered voluntary confidential testing.

• A system for distribution and supply of antiretroviral therapy and breastmilk substitutes must be organized. Regular supply, secure storage, distribution and accounting need to be organized. Zidovudine (ZDV) is now included in the WHO Model List of Essential Drugs. The regimen is set out in table 1.

• Upon introduction of antiretroviral therapy, monitoring and evaluation of safety and efficacy should be in place. Factors of operation and efficacy should also be addressed.

The successful implementation of an antiretroviral regimen and a decrease in vertical transmission will depend on the number of women consenting to testing and returning for the results, on the simplicity of the regimen, and the ease with which they can return for follow-up. Further information concerning the implementation of anti-HIV therapy is available from WHO and UNAIDS.

References


Malaria Researchers!

Letters of interest are invited from researchers conducting projects on the discovery and development of drugs against malaria

Please contact:
MMV/TDR
World Health Organization
CH 1211 Geneva 27, Switzerland
e-mail: mmv@who.ch
fax: 41 22 791 4854
Recommendations from the Expert Committee on Drug Dependence

Efforts to provide an international legal framework for the control of psychoactive drugs have resulted in the formulation of the 1961 Single Convention on Narcotic Drugs and the 1971 Convention on Psychotropic Substances. Both are major achievements in the development of coordinated international control of dependence-producing drugs. The international drug control treaties are instruments which provide a framework for the regulation of a number of defined narcotic drugs and psychotropic substances, the most dangerous of which are eliminated from use. Those that are potentially beneficial are subjected to controls in production, manufacture, trade and distribution so that their use can be limited exclusively to scientific or medical purposes. Details of the scheduling are set out in the table on page 228.

Each Convention embodies a policy and indicates the type of legislation and drug regulatory control to be administered. These controls are intended to ensure the availability for legitimate use of the controlled substances and prevent their abuse. The Conventions assign to WHO the responsibility for recommending their placement in the appropriate schedules for control purposes and proposing amendments to such schedules. The WHO Expert Committee on Drug Dependence is charged with assessing the dependence liability and therapeutic usefulness of each substance. Following evaluation of the seriousness of the public health and social problems related to possible abuse, WHO makes a recommendation to the Commission on Narcotic Drugs.

At the thirty-first meeting of the WHO Expert Committee on Drug Dependence held in June 1998 a number of dependence-producing psychoactive substances were reviewed in order to decide on their public health impact and status in relation to the Conventions. The following substances were recommended for scheduling or review.

Dihydroetorphine is a potent µ-opioid receptor agonist. Approved for marketing in China for the relief of acute severe pain, it is currently a controlled drug in that country. Based on its pharmacological properties and high dependence potential, the Expert Committee estimates that it is equivalent in abuse potential and effects to other drugs already placed in Schedule I of the 1961 Single Convention on Narcotic Drugs.

Remifentanil is a selective µ-opioid receptor agonist with an ultra-short duration of action which has been approved for marketing in 17 countries. It is used medically as an analgesic for induction and maintenance of general anaesthesia, for continuation of anaesthesia into the immediate postoperative period under the direct supervision of an anaesthetist or in an intensive care setting, or as an analgesic component of monitored anaesthesia care.

In terms of review criteria under the 1961 Convention, opioids are calibrated and ranked against morphine to determine abuse potential. Based on the pharmacological properties and dependence potential of remifentanil, the Committee agreed that abuse liability and the ill-effects profile are similar to those of drugs placed on Schedule I of the Convention. It was therefore recommended that remifentanil be placed in Schedule I.

With regard to recommendations for scheduling under the 1971 Convention on Psychotropic Substances, the Committee reviewed the current status of ephedrine use and abuse. The public health and social problems associated with the abuse of ephedrine appear to be significant, particularly in certain African countries. It was therefore recommended that l-ephedrine and the racemate be placed in Schedule IV of the 1971 Convention. The d-isomer is significantly less potent than the l-isomer.

In making this recommendation, the Committee noted that combination products containing ephedrine may be eligible for exemption from scheduling under the terms of the 1971 Convention.

A proposal was submitted to the Committee concerning the scheduling of isomers, esters, ethers and pharmacological analogues of the psychotropic substances currently controlled in Schedules I and II of the 1971 Convention. With regard to the sched-