

Impact of vaccination on selected diseases in Canada

Stanley E. Acres, MD, DPH
Paul V. Varughese, DVM, MSc

Vaccination has dramatically reduced the morbidity and mortality rates of a number of diseases. The crucial element of vaccination programs is commitment to widespread coverage and to containment of outbreaks. Vaccines have led to virtual elimination of poliomyelitis and promise to eliminate measles. The incidence of congenital rubella syndrome will probably only be diminished if vaccination is extended to all 1-year-olds and susceptible prepubertal girls. The employment of diphtheria toxoid is one of the great success stories in public health. The incidence of pertussis has declined because of the diphtheria-pertussis-tetanus (DPT) vaccine given to infants, although elimination of the disease will probably have to await development of a more potent pertussis antigen. A remarkable reduction in the incidence of tetanus and tuberculosis has also been achieved.

Les vaccins ont abaissé de façon dramatique la morbidité et la mortalité de plusieurs maladies. Les principaux éléments d'un programme de vaccination sont l'application au plus grand nombre de sujets possible et la limitation des épidémies. Grâce aux vaccins, on a assisté à la disparition quasi-complète de la poliomyélite, et on peut s'attendre à la même chose pour la rougeole. Quant à la rubéole congénitale, sa fréquence ne s'abaissera que si on vaccine tous les enfants à l'âge de 1 an et toutes les

From the Bureau of Epidemiology, Laboratory Centre for Disease Control, Department of National Health and Welfare, Ottawa

Reprint requests to: Dr. Stanley E. Acres, Chief, Communicable Diseases Division, Bureau of Epidemiology, Laboratory Centre for Disease Control, Tunney's Pasture, Ottawa, Ont. K1A 0L2

filles d'âge prépubertaire dépourvues d'immunité rubéoleuse. L'anatoxine diphtérique est l'un des triomphes de la médecine préventive. Si la vaccination des nourrissons par le DCT (diphthérie-coqueluche-tétanos) a abaissé la fréquence de la coqueluche, cette maladie ne sera probablement éliminée que lorsque nous disposerons d'un antigène coquelucheux plus efficace. On a assisté également à une baisse remarquable de la fréquence de la tuberculose et du tétanos.

Immunization programs in Canada fall within the jurisdiction of the 10 provincial departments of health, although the Department of National Health and Welfare assumes responsibility for the two territories. The lack of a single authority has sometimes led to confusion among both the public and the health professions about preferred vaccine, number of doses required to ensure immunity, and age for administration. In three provinces (Alberta, Saskatchewan and Prince Edward

Island) virtually all childhood vaccination is carried out by public health departments, while in the other provinces private practitioners perform half or more of all immunization procedures. In spite of this mixed delivery system, Canada has achieved a remarkably good record in controlling the vaccine-preventable diseases.

The following review is based on notifiable disease statistics from Statistics Canada and from within the Bureau of Epidemiology.

Poliomyelitis

Poliomyelitis has been a notifiable disease in Canada since 1924. Fig. 1 shows the annual incidence rates of paralytic polio since 1949; the last major epidemic occurred in 1959, when 1887 cases were reported. Following the introduction of inactivated polio vaccine (IPV) in 1955 and oral polio vaccine (OPV) in 1962, the annual number of reported cases dropped dramatically. Indigenous polio appears to have been eliminat-

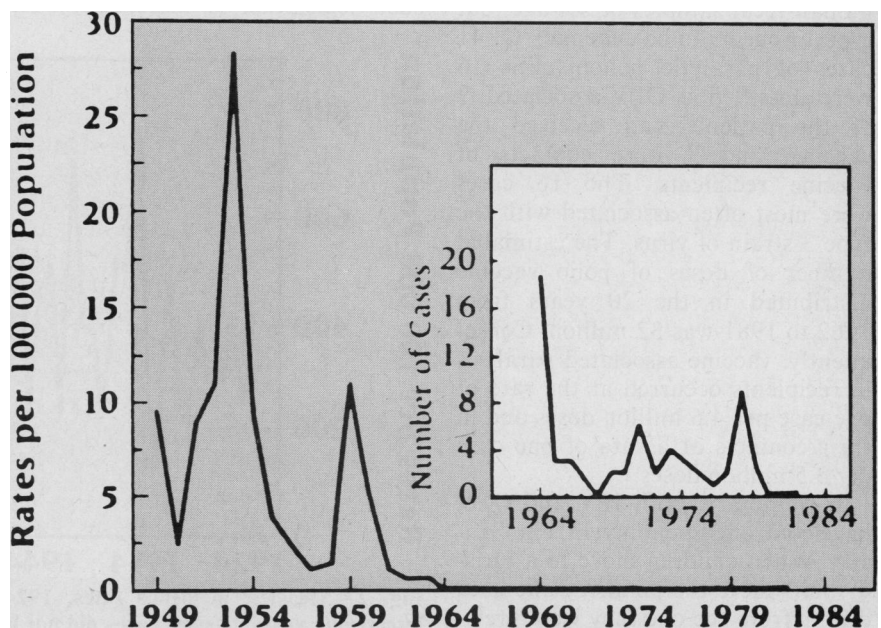


Fig. 1—Paralytic poliomyelitis: incidence rates and numbers of reported cases, 1949 to 1982.

ed, with no cases reported in Canada from 1980 through 1984.

From 1955 to 1957, more than 6 million doses of IPV were administered. Following licensure of OPV in 1962, all provinces except Ontario and Nova Scotia switched to its use. Most provincial epidemiologists at that time were convinced that OPV was superior because it stimulated within the intestinal tract the production of secretory antibody similar to that induced by natural infection. An added benefit of OPV was considered to be the fecal excretion of vaccine strains, leading to indirect immunization of close contacts.

However, virologic evidence from the National Capital Region of Ottawa-Hull indicates that the numbers of individuals indirectly immunized are not as great as one might expect. In Hull OPV is used, while in Ottawa IPV is used. Several thousand Quebec children are treated annually along with their Ontario counterparts at the Children's Hospital of Eastern Ontario in Ottawa, but studies of stools from inpatients at this hospital showed the presence of OPV strains only in the Quebec children.^{1,2} Either the live attenuated strains in OPV do not spread in the environment of a children's hospital or the high rate of previous vaccination with IPV limits their dissemination.

Since 1964, wild poliovirus types 2 and 3 have not been detected in human fecal samples or sewage, but type 1 appears to be endemic.³ Of 41 cases of paralytic poliomyelitis 16 were classified as OPV-associated; 7 of the patients had received the vaccine, and 9 were contacts of vaccine recipients. The 16 cases were most often associated with the type 3 strain of virus. The estimated number of doses of polio vaccine distributed in the 20 years from 1962 to 1981 was 32 million. Consequently, vaccine-associated paralysis in recipients occurred at the rate of one case per 4.6 million doses and in their contacts at a rate of one case per 3.5 million doses.

In summary, both IPV and OPV have controlled poliomyelitis in Canada. When children move to a jurisdiction where the polio vaccine used differs from the one they were previously given, they may continue their immunization schedule with the

other vaccine rather than restart the series, according to the National Advisory Committee on Immunization.⁴

Measles

Measles has exhibited epidemic peaks in Canada every 2 to 3 years. The highest annual number of cases reported was 83 000, in 1935 (Fig. 2). The average annual incidence rate during the 10 years from 1949 through 1958 was 358 cases per 100 000 population, whereas that for 1974 through 1983 was only 38 — a reduction of 89%. In 1983, infants had the highest incidence rate; preschoolers were next.

Measles vaccine has been in use in Canada since the mid-1960s. Several types have been used, including inactivated vaccine, but all provinces now routinely use an attenuated vaccine with strains of measles, mumps and rubella viruses (MMR) for children between 12 and 15 months old.

Ontario and New Brunswick, representing 39% of Canada's population, introduced legislation in 1981 and 1982 respectively making measles vaccination compulsory for school attendance. Students who do not show proof of vaccination against measles and who have not been granted exemption on religious, medical or philosophic grounds can be barred from school. Most provincial epidemiologists believe that such legislation is unnecessary for

high levels of coverage. Some provinces report that up to 98% of children are vaccinated by the time they reach school age. At school enrolment pupils in the other provinces are usually requested to show proof of vaccination, even though this is not required by law. The merit of compulsory, compared with voluntary, immunization programs is difficult to evaluate at present: while legislation undoubtedly ensures continued high levels of coverage, voluntary programs in provinces that have a commitment to screen and vaccinate susceptible children have also proved successful.

Rubella

In the prevaccine era the rubella incidence rate in Canada peaked irregularly every 3 to 10 years, with the highest rate recorded in 1936, when nearly 70 000 cases were reported.

Following inception of vaccination programs in the early 1970s the annual numbers of cases of rubella showed a marked decline. Health authorities in seven provinces chose mass vaccination of all 1-year-olds, whereas those in Alberta, Saskatchewan and Manitoba instituted vaccination of prepubertal girls.

Although these policies were maintained for almost a decade, there was no evidence that one approach was superior to the other in terms of reduced numbers of cases

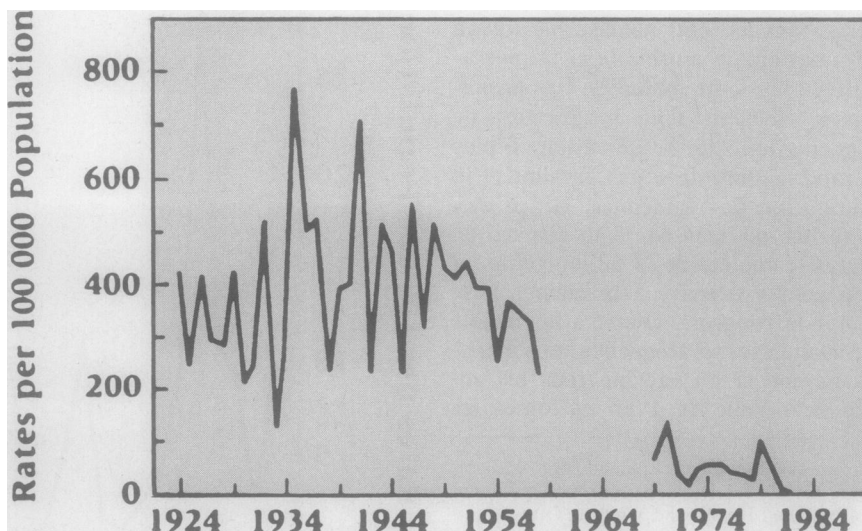


Fig. 2—Measles: incidence rates, 1924 to 1958 and 1968 to 1982. During the intervening years measles cases did not have to be reported to national authorities; in 1963 live vaccine was licensed, and a year later an inactivated vaccine became available.

of congenital rubella syndrome (CRS). A total of 67 CRS cases were reported from 1979 to 1983, and over half of these cases occurred in 1979. Only 3 to 15 cases have been reported annually since 1980.

The National Advisory Committee on Immunization expressed no preference in the 1970s for one policy or the other, endorsing both.⁵ In 1982 it revised its recommendations and advocated routine vaccination of all infants at 12 months; all prepubertal girls who lack documen-

tary evidence of vaccination, and all susceptible adolescent and adult women of child-bearing age.⁶ This comprehensive policy, if implemented throughout Canada, should markedly reduce the incidence of CRS in the shortest possible time. In 1983 all provinces adopted the policy of routine MMR vaccination of infants at 12 to 15 months of age. Six provinces also routinely administer rubella vaccine to prepubertal girls regardless of past immunization history.

Diphtheria

National notification of diphtheria began in 1924, and the greatest annual number of cases (9000) was recorded that year. The morbidity and mortality rates dramatically declined following commencement of toxoid administration, in about 1930 (Fig. 3). In 1983 only 11 cases were reported, and there have been no deaths reported since 1981.

Still, toxigenic strains of diphtheria bacilli are detected in the pharynx, skin and ears of considerable numbers of diphtheria carriers in northern and western Canada. Classic diphtheria is now seen only as a disease of the unimmunized or partially immunized.

Tetanus

Likewise, tetanus has shown a remarkable decline in both morbidity and mortality rates (Fig. 4). Currently about 20 persons are hospitalized annually in Canada for treatment of tetanus. Over the past 5 years, of the seven deaths recorded, five were of persons over 60 years of age.

The rate of decline in the tetanus mortality rate prior to the 1960s was greatest in two periods. The first was 1941 to 1945, when a 53% overall reduction occurred compared with the preceding 5-year period. This was probably related to the extensive use of tetanus toxoid in the Canadian Armed Forces beginning in 1939. Among Forces personnel during the Second World War, only three people were reported to have contracted tetanus, and one was known to be inadequately immunized.⁷

The second substantial decline in the mortality rate (59%), between 1956 and 1960, may be attributed partly to the use since 1948 of the combined diphtheria-pertussis-tetanus (DPT) vaccine for preschoolers. Tetanus can be prevented only by individual immunization since "herd immunity" plays no part in control. Continuing vaccination of the total population is necessary.

Pertussis

Pertussis has also been a notifiable disease in Canada since 1924. It

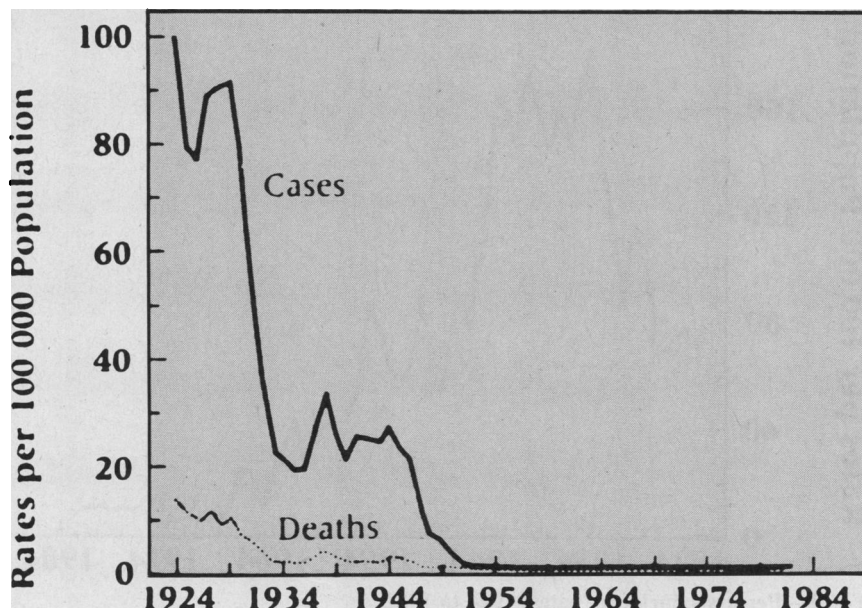


Fig. 3—Diphtheria: incidence and mortality rates, 1924 to 1982.

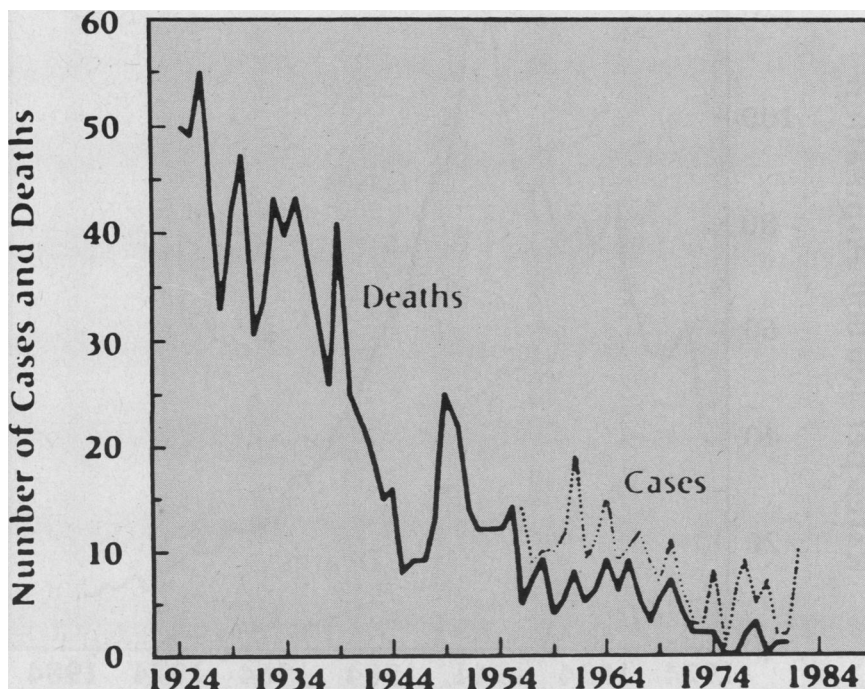


Fig. 4—Tetanus: incidence and mortality rates, 1924 to 1982.

has exhibited epidemic peaks in cycles of 3 to 5 years (Fig. 5). The incidence rates were remarkably high in the 1930s and early 1940s, then declined coincident with the introduction of combined diphtheria-pertussis (DP) vaccine in 1943. Published reports on field trials in Quebec⁸ and Alberta⁹ in 1943 through 1945 showed that the pertussis vaccine effectively reduced morbidity and mortality rates, with unvaccinated children exhibiting infection 28 to 30 times as often as vaccinated children. Most of the provinces subsequently adopted a DP immunization program, although the level of coverage on a historical basis is not known. In the 1980s the incidence rates of pertussis have been about one third of those observed in the 1960s.

Infants have suffered the highest attack rates in both epidemic and non-epidemic years. Since 1967, children 1 to 4 years old have ranked second, followed by the 5- to 9-year-olds. Infants have also had the highest hospitalization rates and the longest hospital stays. Between one and four children die from pertussis complications in Canada every year — most in the first year of life.

Although a remarkable reduction in incidence has been achieved, well over 2000 cases of pertussis are still reported annually in Canada. Bacteriologic confirmation is not obtained in a large proportion of cases, some of which are probably caused by *Bordetella parapertussis*, adenovirus, echovirus, coxsackievirus, respiratory syncytial virus, *Chlamydia* and *Haemophilus influenzae*. The elimination of pertussis will probably have to await development of a more potent vaccine antigen.

Tuberculosis

Morbidity and mortality rates for tuberculosis have declined greatly in Canada in the last few decades (Fig. 6). The incidence of tuberculosis varies from one geographic region to another and is highest in native (Indian, Inuit and Métis) populations, in men over 40 and in immigrant groups from countries with a high incidence of the disease.

More than 2000 new cases are still diagnosed annually. Persons born outside Canada account for

more than one third, and of this group 40% have arrived in Canada within the past 5 years. About 60% have emigrated from Asia and 30% from Europe.

The National Advisory Committee on Immunization now recommends bacille Calmette-Guérin (BCG) vaccine only for the following selected persons and groups:¹⁰

- Individuals who are repeatedly exposed to untreated or inadequately treated active tuberculosis.
- Communities or groups of per-

sons with a high rate of infection, including Indian, Métis and Inuit children, in which other control measures have proven ineffective.

- Health workers at a considerable risk of exposure to unrecognized infectious pulmonary tuberculosis or who handle tubercle bacilli or potentially infectious specimens in a laboratory.

- Newborn infants whose mothers have infectious tuberculosis at the time of delivery, although isoniazid (INH) prophylaxis is preferred

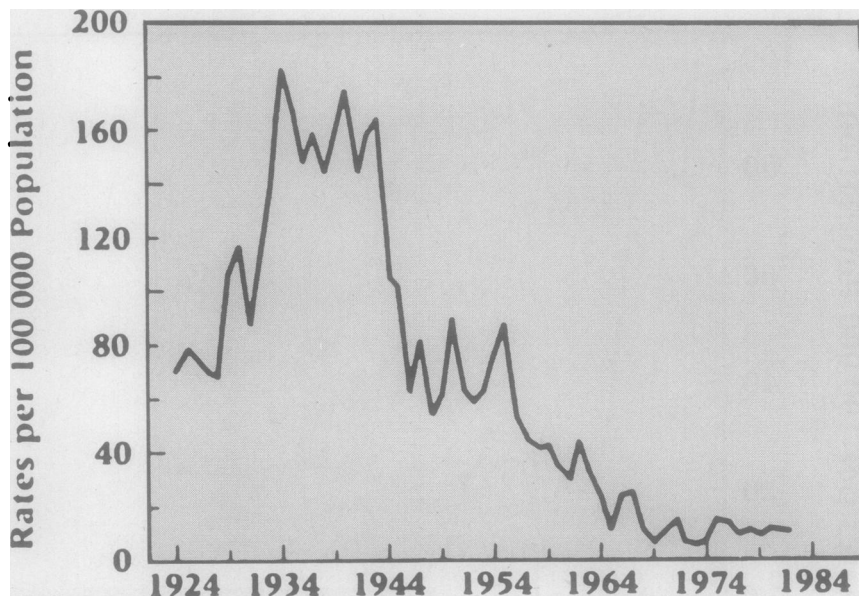


Fig. 5—Pertussis: incidence rates, 1924 to 1982.

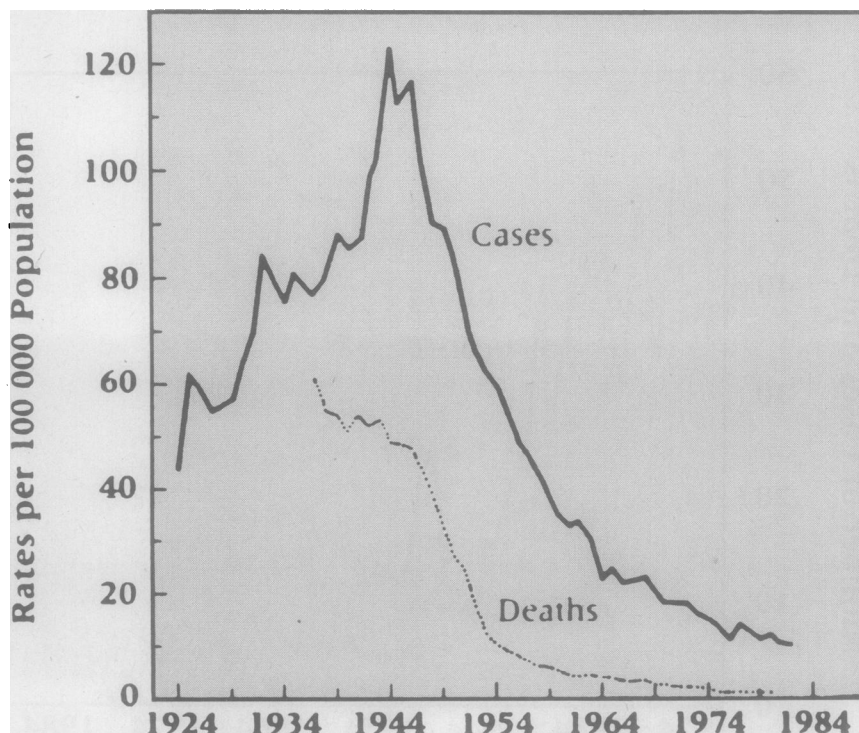


Fig. 6—Tuberculosis: incidence and mortality rates, 1924 to 1982.

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(hydralazine hydrochloride)
Antihypertensive Agent

to avoid the necessary separation of mother and infant when BCG is used. However, BCG is recommended if the infecting strain is INH-resistant or if compliance with a program of INH prophylaxis cannot be assured. BCG may also be considered for the infant after INH prophylaxis is completed, provided chest radiographs are normal and the result of a tuberculin test is negative.

With the declining incidence of tuberculosis in Canada, the elderly and immigrant groups have become the major foci of disease transmission; however, control of the disease in these groups is sometimes complicated by difficulty in diagnosis and poor patient compliance with therapeutic regimens. Also, physicians rarely suspect tuberculosis when making a differential diagnosis, so continuing surveillance is needed.

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Actions

Hydralazine hydrochloride exerts its hypotensive action by reducing vascular resistance through direct relaxation of vascular smooth muscle.

Indications

APRESOLINE Oral: Essential hypertension. APRESOLINE is used in conjunction with a diuretic and/or other antihypertensive drugs but may be used as the initial agent in those patients in whom, in the judgment of the physician, treatment should be started with a vasodilator.
APRESOLINE Parenteral: Severe hypertension when the drug cannot be given orally or when there is an urgent need to lower blood pressure (e.g. toxemia of pregnancy or acute glomerulonephritis). It should be used with caution in patients with cerebral vascular accidents.

Contraindications

Hypersensitivity to hydralazine, coronary artery disease, mitral valvular rheumatic heart disease, and acute dissecting aneurysm of the aorta.

Warnings

Hydralazine may produce in a few patients a clinical picture simulating systemic lupus erythematosus, in such cases treatment should be discontinued immediately. Long-term treatment with adrenocorticosteroids may be necessary. Complete blood counts, L.E. cell preparations, and antinuclear antibody titer determinations are indicated before and periodically during prolonged therapy with hydralazine and if patient develops arthralgia, fever, chest pain, continued malaise or other unexplained signs or symptoms. If the results of these tests are abnormal, treatment should be discontinued.

Usage in Pregnancy

Animal studies indicate that high doses of hydralazine are teratogenic. Although there is no positive evidence of adverse effects on the human fetus, hydralazine should be used during pregnancy only if the benefit clearly justifies the potential risk to the fetus.

Precautions

Caution is advised in patients with suspected coronary artery disease, as it may precipitate angina pectoris or congestive heart failure, and it has been implicated in the production of myocardial infarction. The "hyperdynamic" circulation caused by APRESOLINE may accentuate specific cardiovascular inadequacies, e.g. may increase pulmonary artery pressure in patients with mitral valvular disease. May reduce the pressor responses to epinephrine. Postural hypotension may result. Use with caution in patients with cerebral vascular accidents and in patients with advanced renal damage. Peripheral neuritis has been observed and published evidence suggests an antipyridoxine effect and the addition of pyridoxine to the regimen if symptoms develop.

Blood dyscrasias consisting of reduction in hemoglobin and red cell count, leukopenia, agranulocytosis and purpura have been reported. In such cases the drug should be withdrawn. Periodic blood counts are advised during therapy. MAO inhibitors should be used with caution in patients receiving hydralazine. Slow acetylators should probably receive no more than 200 mg of APRESOLINE per day. When a higher dose is contemplated, and, whenever possible, it may be advisable to determine the patient's acetylation phenotype.

Adverse Reactions

Within the first day or two: headache, palpitations, tachycardia, anorexia, nausea, vomiting, diarrhea, and angina pectoris. They are usually reversible when dosage is reduced or can be prevented or minimized by administering reserpine or a beta-blocker together with hydralazine.

Less Frequent: nasal congestion; flushing; lacrimation; conjunctivitis; peripheral neuritis, evidenced by paresthesias, numbness, and tingling; edema; dizziness; tremors; muscle cramps; psychotic reactions characterized by depression, disorientation, or anxiety; hypersensitivity (including rash, urticaria, pruritus, fever, chills, arthralgia, eosinophilia, and, rarely hepatitis); constipation; difficulty in micturition; dyspnea; paralytic ileus; lymphadenopathy; splenomegaly; blood dyscrasias, consisting of reduction in hemoglobin and red cell count, leukopenia, agranulocytosis, thrombocytopenia with or without purpura; hypotension; paradoxical pressor response.

Late Adverse Reactions: Long-term administration at relatively high doses may produce an acute rheumatoid state. When fully developed a syndrome resembling disseminated lupus erythematosus occurs. The frequency of these untoward effects increases with dosage and duration of exposure to the drug and is higher in slow than in fast acetylators. Antinuclear antibody and positive L.E.-cell tests occur.

Symptoms and Treatment of Overdosage

Symptoms: hypotension, tachycardia, headache, generalized skin flushing, myocardial ischemia and cardiac arrhythmia can develop. Profound shock can occur in severe overdosage.

Treatment: No known specific antidote. Evacuate gastric content, taking adequate precautions against aspiration and for protection of the airway; if general conditions permit, activated charcoal slurry is instilled. These procedures may have to be omitted or carried out after cardiovascular status has been stabilized, since they might precipitate cardiac arrhythmias or increase the depth of shock.

Support of the cardiovascular system is of primary importance. Shock should be treated with volume expanders without resorting to use of vasopressors, if possible.

If a vasopressor is required, a type that is least likely to precipitate or aggravate cardiac arrhythmia should be used, and the E.C.G. should be monitored while they are being administered.

Digitalization may be necessary. Renal function must be monitored and supported as required.

No experience has been reported with extracorporeal or peritoneal dialysis.

Dosage and Administration

Adjust dosage according to individual blood pressure response.

Orally: Initial: 10 mg 4 times daily for the first 2 to 4 days, 25 mg 4 times daily for the remainder of the first week, 50 mg 4 times daily for the second and subsequent weeks of treatment.

Maintenance: adjust dosage to lowest effective levels. Following titration, some patients may be maintained on a twice daily schedule.

Usual maximum daily dose is 200 mg, up to 300 mg daily may be required in some patients. In such cases a lower dosage of APRESOLINE combined with a thiazide, reserpine or both, or with a beta-adrenergic-blocking agent may be considered. When combining therapy, individual titration is essential to ensure that the lowest possible therapeutic dose of each drug is administered.

Parenterally: patients should be hospitalized. Usual dose is 20-40 mg I.M. or by slow I.V. injection or I.V. drip, repeated as necessary. Patients with marked renal damage may require a lower dosage.

For I.V. drip, the ampoule(s) should be added to 5% sorbitol solution, physiological saline or Ringer solution; glucose solution is not suitable for this purpose. Blood pressure levels should be monitored. It may begin to fall within a few minutes after injection, with an average maximal decrease occurring in 10 to 80 minutes. In cases with a previously existing increased intracranial pressure, lowering the blood pressure may increase cerebral ischemia.

Most patients can be transferred to oral APRESOLINE within 24 to 48 hours.

Availability

Tablets of 10 mg: yellow, uncoated, biconvex, scored, and imprinted "FA" on one side and "CIBA" on the other.

Bottles of 100 and 500.

Tablets of 25 mg: blue, coated, printed "GF" on one side and "CIBA" on the other.

Bottles of 100 and 500.

Tablets of 50 mg: pink, coated, printed "HG" on one side and "CIBA" on the other.

Bottles of 100 and 500.

Ampoules: 1 ml, each containing 20 mg hydralazine hydrochloride, 103.6 mg propylene glycol, 0.65 mg of methyl-p-hydroxybenzoate and 0.35 mg of propyl-p-hydroxybenzoate in water for injection.

Boxes of 10.

Complete Prescribing Information available on request.

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Mississauga, Ontario
L5N 2W5

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