Subarachnoid Hemorrhage in New Zealand: An Epidemiological Study

RUTH BONITA, B.A., DIP.ED., M.P.H.,* ROBERT BEAGLEHOLE, M.D., F.R.A.C.P.,†
AND J. D. K. NORTH, D.PHIL., F.R.C.P.*

SUMMARY. To examine long-term trends in subarachnoid hemorrhage (SAH) mortality and morbidity, an analysis of routinely available information is presented for the 20 year period from 1959. To document the current incidence and case fatality of SAH, the results of a large scale community-based study in the Auckland region are presented. SAH mortality rates for both men and women, especially women, have declined since the mid-1970's. The decline appears to be real, and is most striking in the 45–64 year age groups. A corresponding decline in discharge rates from hospital has also occurred in these age groups. In contrast, cases fatality rates have remained stable at about 42% for the 20 year period under review. The community-based study identified 92 cases in a total population of 829,464 in a twelve month period. The age standardised incidence rates were 13.4 and 15.8 per 100,000 for men and women respectively. In the age group 25–35 years, the incidence rate was particularly high at 8.5/100,000. Case fatality at 28 days was 52%. A decline in incidence appears the most likely explanation for the overall decline in national mortality.

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Subarachnoid Hemorrhage (SAH) is an important sub-category of cerebrovascular disease (CVD) because of its high mortality and its relatively frequent occurrence in young people. It is usually caused by rupture of an aneurysm, and unlike other types of stroke, diagnostic procedures more frequently confirm the clinical diagnosis. Death rates for all categories of CVD in New Zealand are declining, particularly among women,¹ and in this paper data on SAH mortality and morbidity in New Zealand for the past 20 years are examined to determine if the SAH trends follow a similar pattern. Baseline data on the incidence and case fatality at one month of SAH from a large community-based study of cerebrovascular disease in Auckland, New Zealand, are also presented.

Methods

(a) National Mortality and Morbidity Data

Between 1959 and 1968 SAH was classified under rubric 330 of the seventh revision of the International Classification of Diseases (ICD) and since then under rubric 430 in the eighth and ninth revisions. This change has had no effect on classification rules. Data on mortality and morbidity from SAH by age and sex, together with corresponding population figures, for the 20 year period from 1959, were provided by the National Health Statistics Centre.² These cases were grouped into triennial periods and the age specific rates were calculated using the population for the mid-year of the period as the denominator. Mortality and hospital morbidity rates were then age standardised by the direct method to the total 1951 New Zealand population and expressed as average annual rates per 100,000 population. To identify false positives in national mortality data, all deaths certified as due to SAH in Auckland during the year beginning 1st March 1981 were identified. Information from the medical records of these cases was examined to determine if the inclusion criteria for this study were met.

Annual case fatality rates for the 20 year period 1959–1979 were estimated using all deaths from SAH in a calendar year as the numerator, and the sum of all SAH discharges from hospital, SAH deaths occurring in hospital, and SAH deaths occurring outside hospital in that calendar year as the denominator. This calculation is based on the assumption that most deaths outside hospital occur before hospitalization could be arranged and that all other non-fatal cases are admitted to hospital.

(b) Auckland Incidence Study

All cases of SAH in residents of the Auckland region (1981 census population 829,464) during a twelve month period from the 1st March 1981 were identified as part of the Auckland Region Coronary and Stroke (ARCOS) study. Primary SAH was defined as a spontaneous rupture of an aneurysm or arteriovenous malformation (AVM) leading to bleeding into the subarachnoid space. In the absence of an accepted standard definition, the following diagnostic criteria have been used: abrupt onset of a severe headache and/or impaired consciousness or focal neurological features associated with at least one of the following clinical signs: lumbar puncture findings of uniform blood-staining and xanthochromia of the cerebrospinal fluid (CSF); computerised axial tomography (CT scan) evidence of blood in the subarachnoid space; cerebral angiographic identification of an aneurysm or AVM at surgery or autopsy. This definition excludes primary intracerebral haemorrhage with secondary rupture into the subarachnoid space, or rupture due to trauma, neoplasms or infections.

Multiple sources of case-finding were used including daily searches of hospital admission lists, visits to neurosurgical and neurological wards of the three main hospitals in Auckland, together with a systematic search of hospital discharges, postmortem and coroners’ reports and death certificates. A representative sample (51% or 231) of the general practitioners in the Auckland region also referred suspected cases from...
their practices to provide an estimate of the number of non-hospitalised cases. Information concerning the current event, patterns of management, diagnostic investigation, past medical history as well as socio-demographic variables, was obtained by one trained nurse-interviewer using a standardised questionnaire. The interview was conducted with the patient when possible, otherwise with a close family member.

Results

(a) National Mortality and Morbidity Trends

There were 191 deaths from SAH in New Zealand in 1979 of which 60% occurred in women, and these accounted for 6.6% of all CVD deaths. In contrast to deaths from other categories of CVD where only 16% occur under the age of 65 years, 62% of deaths from SAH occur below this age. Reasonable confidence can be placed in the national mortality data since a partial validation of all deaths certified as due to SAH in the Auckland region for the twelve month period beginning 1st March 1981 indicated that 92% met the criteria used in the incidence study.

Age standardised SAH mortality rates for ages 25 years and over for the period 1959-1979 are presented in figure 1. The rates are consistently higher for women than for men, and follow a different trend in the two sexes. Male death rates remained relatively steady at around 10.6 per 100,000 until 1972, and since then they have declined slightly to 8.7 per 100,000. Women, however, experienced a gradual increase in death rates, reaching a peak of about 17.5 per 100,000 around 1969, followed by a decline starting in the early 1970's and reaching 14.2 per 100,000 in 1977-79. The decline in the five year period 1975-1979 was from 9.4 to 8.3 per 100,000 and from 18.6 to 11.9 per 100,000 for men and women respectively.

Age specific rates (fig. 2) indicate that the downward trend occurred only among those less than 65 years, so that the decline for those aged 25-64 is thus much higher: 24% for men and 48% for women in the same period. Mortality increases with age: there was only a three- to fourfold increase from 10 per 100,000 at ages 35-44 years, to 35 per 100,000 at 65 years and above in contrast to all other categories of stroke in which the rates increase more than one hundred with increasing age. Women experience death rates that are almost 50% higher than men in all age groups. The estimated national case fatality rates did not change throughout the 20 year period. In the triennial period 1959-61 the case fatality was 42% compared with 41% in 1977-79.

Age standardised hospital morbidity rates (those discharged from or dying in public hospitals) for the period 1959-1979 are presented in figure 3. A decline of 15% occurred for both men and women 25 years and over since the 1974-76 triennium. The trend is similar to that observed for death rates, especially for women. Further analysis of age specific rates indicates that this decline occurred in each age group below 65 years and in both sexes (fig. 4). This corresponds with the improvements in mortality, particularly among women, in the younger age groups.

(b) Auckland Incidence Study

Case-finding and Diagnostic Procedures

Of the 92 cases registered, 40% were found through a combination of sources; almost half (45%) were identified solely through hospital admissions and discharges (table 1). All who survived 24 hours had been admitted to hospital; however, coroners' and postmortem reports revealed 14 cases who died before reaching hospital. Autopsy was performed on 69% of all those patients who died. Table 2 shows the particular proce-
Incidence and Case Fatality

The age and sex specific incidence and case fatality rates at 28 days are presented in table 3. There were 13 non-Europeans (14% of the total number) but no attempt was made to analyse race separately because of the small numbers involved. The 40 men and 52 women identified represent an age standardised incidence of 13.4 and 15.8 per 100,000 for men and women respectively. Men had a higher incidence than women until 35 years but thereafter the incidence rates were higher for women. The median age was 42 years for men and 57 years for women; 38% of men were under the age of 35 years compared to only 4% of women.

Case fatality rate within the first 48 hours was 37% and within the first week 39%; 52% had died within the first 28 days. Women experienced a higher case fatality rate (62%) than men (40%), but this difference was not statistically significant (Mantel-Haentzel chi square 2.76, p = 0.1).

Discussion

(a) National Mortality and Morbidity Trends

Mortality

In both sexes and all age groups less than 65 years, SAH mortality has declined since 1975. This improvement does not appear to be an artefact due to changes in diagnostic fashion or ICD coding classification. SAH is a well-defined entity and the ICD classification has not changed in the period reviewed. More than any other sub-category of stroke, reliable objective investigation allows a precise diagnosis of SAH. Furthermore, the rates for all sub-groups of CVD, including intracerebral haemorrhage, have declined for the same period.1 A partial validation of death certificates in Auckland in 1981–82 confirmed that in 92% of the cases, when objective criteria were applied, the diagnosis was sustained. However, evidence from the Auckland study suggests that national mortality data for those over 65 years may be less reliable since autopsies are less likely to be performed on elderly patients.

There appears to be only one other report of trends in national SAH mortality. Unlike the mortality pattern in New Zealand, in England and Wales the mortality rates increased for the period 1959–73, particularly among males who also increased their share of SAH deaths.4

Morbidity

Hospital morbidity data is useful as a measure of SAH incidence in New Zealand, since it is known from the Auckland study that all SAH patients who survived a significant initial bleed were admitted to hospital. Hospital morbidity rates were relatively stable in New Zealand, at least in the decade prior to 1974. Since then, however, there has been a 16% decline, and while not as great as that observed for the decline in mortality rates, it nevertheless suggests that fewer new cases are occurring. An estimate of case fatality rates supports this impression since no improvement ap-
peared to occur during the 20 year period under review. Thus, the most likely explanation for the recent decline in SAH mortality is a decline in incidence. It is possible that whatever has caused the decline in mortality rates of other categories of stroke may, in the New Zealand population, have also affected SAH.

The age adjusted average annual incidence of SAH has remained virtually constant in Rochester, Minnesota, from 1945 to 1974, whereas there was a decline in incidence of other categories of stroke in that population. Thus, whatever caused this decline it did not affect the incidence of SAH. On the basis of the recent improvements in New Zealand mortality and morbidity, it is postulated that an update of the Rochester data would reveal a decline in their incidence rates. In a much smaller study in Washington County, Maryland, no real decline in incidence of SAH occurred in the period 1969/71 to 1974/76, although a significant decline occurred in intracerebral haemorrhage.

(b) Auckland Incidence Study

Auckland is well suited for studying the epidemiology of SAH. The area has a well-defined population comprising one quarter of New Zealand’s total population, all sources of medical care can be identified, and medical records are readily accessible. There is good reason to believe that sources of case-finding were comprehensive. However, the number of false negatives is not known, and it is possible that an underestimation of the incidence of SAH occurred in those over the age of 65 years. Five elderly women with a clinical history consistent with SAH were certified as having died of SAH, but in the absence of objective investigations, the diagnosis could not be confirmed, and these cases were not included. This may explain the fact that SAH incidence in the Auckland study did not increase with increasing age to the oldest age groups as reported elsewhere.

Comparison with other studies is hampered by lack of an agreed criteria for SAH. Some studies, including the Auckland study, stipulate xanthochromia detected by spectrophotometry in addition to uniformly blood-stained CSF, but others accept an atraumatic lumbar puncture yielding uniformly blood-stained CSF. Some accept focal neurological deficit at onset and others excluded cases on this basis. One study made arbitrary decisions of inclusion or exclusion based on age (e.g. all patients over 50 years and hypertensive patients less than 50 years who died of the initial haemorrhage were excluded).

Most studies are hampered by a small annual number of cases which make comparisons, particularly in younger age groups and between sexes, difficult. Table 4 summarises incidence rates reported in several studies. Except for the youngest and oldest age groups, rates are remarkably similar. Rates in those less than 35 years in the Auckland study are higher than those reported in other countries except for Finland. Rates for those over the age of 65 years are lower; this might be explained by stricter inclusion criteria in the present study. The diagnosis was confirmed by angiography and/or autopsy in 73% of those over the age of 60 years in the Auckland study in comparison with Finland where only 37% of those in this age group were confirmed by these criteria. Rates in Finland are double those in New Zealand in the oldest age group.

Similar high case fatality rates have been noted in other studies. A study of 187 hospital-based cases of SAH indicated that male sex and a poor initial neurological and medical state were the only two variables related to subsequent mortality. The Auckland study, a population-based study, showed no significant difference in outcome between men and women. The Auckland one month case fatality rates are higher than the national one year case fatality rates possibly be-

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**Table 2 Distribution of Supporting Diagnostic Investigations Which Confirmed the Identification of SAH**

<table>
<thead>
<tr>
<th>Lumbar puncture only</th>
<th>CT Scan only</th>
<th>Angiography only</th>
<th>Two or more of above</th>
<th>Autopsy only</th>
<th>Autopsy + lumbar puncture</th>
<th>Autopsy + CT scan</th>
<th>Autopsy + angiography</th>
<th>Autopsy + two or more of above</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>5</td>
<td>4</td>
<td>35</td>
<td>24</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>92</td>
</tr>
</tbody>
</table>

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**Table 3 Incidence and Case Fatality of Subarachnoid Haemorrhage by Sex and Age, Auckland 1981–2**

| Age (years) | Males | | | Females | | | Total | | |
|-------------|-------|------------------|-----------------|------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-------|
|             | Rate* | Case fatality† |       | Rate | Case fatality |       | Rate | Case fatality |       |       |
| 15–24       | 7.9 (6) | 17% | | | | | | | | | |
| 25–34       | 14.4 (9) | 56% | | | | | | | | | |
| 35–44       | 12.1 (6) | 17% | | | | | | | | | |
| 45–54       | 19.7 (8) | 50% | | | | | | | | | |
| 55–64       | 23.1 (8) | 25% | | | | | | | | | |
| 65+         | 8.9 (3) | 100% | | | | | | | | | |
| Age standardised rate‡ | 13.4 (40) | 40% | | | | | | | | | 15.0 (92) | 52% |

* Rates per 100,000 people — number of cases in parentheses.
† At 28 days.
‡ Age standardised by the direct method to the Auckland population, 1981 census.
cause the Auckland SAH patients are a more precisely defined diagnostic group.

The role of diagnostic investigations in the changing trends in SAH mortality is interesting because diagnostic accuracy is a prerequisite for rational therapy and possibly outcome. The introduction of CT scans in the Auckland area in 1977 is the only recent major change in patient management which might affect patient outcome, although it is perhaps too early to assess the effects of this innovation as measured by changes in case fatality rates. It has been reported that the diagnostic accuracy of CT scans is unusually low in SAH patients, confirming the diagnosis in only two-thirds of cases.\(^1\) In the Auckland series, 76% of the CT scans performed on patients indicated that bleeding had occurred. Only a retrospective study of Auckland hospital records of SAH patients will provide information about the impact of changing angiographic and surgical practices, thereby giving some indication of the effect of changes in diagnostic practices over time.

**Conclusion**

The sex differences in changes in mortality over time present intriguing and unresolved issues. The recent decline, particularly in women, appears to be real and follows the same trend as in other categories of stroke.\(^1\) If the death rate which prevailed in 1975 was still current in 1979, then an additional 59 deaths from SAH would have occurred in 1979, most of these to women less than 65 years of age. What factors account for this change? In the absence of data, one can only speculate on the contribution of associated risk factors and/or changes in management. Preceding hypertension is a major risk factor for stroke,\(^4\) however its role in the aetiology of SAH remains controversial.\(^16\) Nevertheless, the greater improvements in mortality among women than in men are in accord with studies which have shown that a higher proportion of women are currently receiving (and using) anti-hypertensive medication than are men.\(^17\) Little is known about community trends in the frequency of other risk factors for SAH such as oral contraceptive use and cigarette smoking,\(^18\) except for census data which suggests that the number of self-reported regular smokers 25–64 years has declined by 3%: from 42% to 39% and from 34% to 31% for men and women respectively in the period 1976 to 1981. Further analysis of the Auckland incidence data with matched controls from an ongoing community-based risk factor study may shed light on these relationships.

Routine available national data provides only an estimate of incidence and case fatality. The Auckland study, a large and well-defined series, establishes a reliable baseline against which any changes in incidence and case fatality of SAH can be compared. A prospective study measuring the incidence, case fatality and management would make it possible to confirm or refute the impression that the declining mortality is a reflection not of improved case fatality rates, but rather a reduction in incidence. Resolution of this question would provide an important contribution to an understanding of the aetiology and management of this serious disease.

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Mechanisms of the Contractile Effect Induced by Uridine 5'-Triphosphate in Canine Cerebral Arteries

YOSHIKI SHIRASAWA, PH.D., RICHARD P. WHITE, PH.D., AND JAMES T. ROBERTSON, M.D.

SUMMARY This study was performed to elucidate mechanisms responsible for the contraction of isolated canine cerebral arteries induced by uridine 5'-triphosphate (UTP) and to ascertain whether UTP given intracisternally causes cerebral arterial constriction. The latter was proven arteriographically to be the case. In vitro, UTP (10^-6 M) and UDP were similar in potency, produced sustained contractions, and were more effective than other pyrimidine nucleotides or uridine. Unlike serotonin (5-HT), UTP was not antagonized by cinanserin and failed to cause constriction of mesenteric arteries. Adenosine similarly antagonized 5-HT and UTP. The Ca^{2+} antagonist nimodipine abolished contractions caused by high K^+ but only incompletely antagonized 5-HT or UTP. On the other hand, procedures that hyperpolarize the cell membrane (low K^+ followed by K^+) abolished tonic contractions induced by UTP. Hyperpolarization prior to UTP (with or without nimodipine) did not, however, prevent the occurrence of a phasic contraction. Papaverine or lanthanum antagonized this phasic response. It was concluded that UTP selectively affects cerebral arteries, may initiate contraction by releasing membrane bound Ca^{2+}, depolarizes the cell membrane to open receptor operated and potential sensitive calcium channels, but does not inhibit the electrogenic Na-pump nor specifically antagonize the vasodilator adenosine.

THE CONCEPT THAT NUCLEOTIDES may regulate vascular tone is based upon numerous studies. It has been proposed that the intracellular nucleotide cyclic adenosine 3', 5'-monophosphate mediates relaxation of vascular smooth muscle and that cyclic quanosine 3', 5'-monophosphate production is associated with contractile responses.1 Recent observations, how­ever, have shown that both of these compounds are associated with relaxation of blood vessels.2 Reports further suggest the nucleoside adenosine is a physio­logical mediator of relaxation for coronary arteries3, 4 and for cerebral arteries of the cat, dog and human.5-7 The vasodilatation caused by adenosine, and closely related compounds, may be linked with the metabolic needs of the heart and brain as well as contribute to migraine.8-9 Although the physiological role of these compounds has not been established, there is agreement that the fundamental effect of purine nucleotides on cerebral arteries is relaxation. In contrast, there is little information concerning the action of pyrimidine nucleotides on the cerebral vasculature.

A report showing that small quantities of uridine 5'-triphosphate (UTP) were present in platelets prompted Urquilla9 to ascertain whether this nucleotide might affect isolated cerebral arteries of the dog and human. The results were remarkable in that UTP produced a prolonged vasoconstriction in these arteries, lasting about 7 and 20 hours, respectively. He suggested that UTP may be a useful tool for studying the mechanisms associated with prolonged vasospasm. Since UTP is evidently present in all cells and the brain is a rich source of this nucleotide (30 μM/100g),10 it is possible that under pathophysiological conditions UTP might contribute to the genesis of vasospasm. Moreover, a preliminary report by Urquilla and coworkers11 showed that UDP likewise caused vasoconstriction and this pyrimidine is ubiquitously present in brain and other tissue. In any case, it is clear that the effects of some pyrimidines on cerebral arteries are diametrically opposite to those produced by purine nucleotides.

From the Departments of Pharmacology and Neurosurgery, University of Tennessee Center for the Health Sciences, Memphis, Tennessee 38163.

Address correspondence to: Dr. Richard P. White, Department of Pharmacology, University of Tennessee Center for the Health Sciences, Memphis, Tennessee 38163.

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R Bonita, R Beaglehole and J D North

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