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ORIGINAL REPORT

Topical Chloramphenicol and the Risk of Acute Leukaemia in Adults

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SUMMARY

Purpose — To investigate the possible role of topical chloramphenicol in the development of adult acute leukaemia.

Methods — The design of the study was a population-based age- and sex-matched case–control study, which collected cases of adult acute leukaemia between 1991 and 1996. Caucasian cases (807) and 1593 Caucasian controls were interviewed in person using a highly structured questionnaire. General practitioner medical records were abstracted for previous topical chloramphenicol use.

Results — 797 cases and 1570 controls were included in the analysis. No association was observed for topical chloramphenicol use and acute leukaemia (adjusted odds ratio, 1-year lag period (OR) 0.91 95% confidence interval (CI) 0.70–1.17). Similar results were observed when the analysis was repeated by diagnostic subgroup and sex. For all the data, a small, non-significant increased risk was observed (OR = 1.21, 95% CI 0.65–2.25) if chloramphenicol had been prescribed three, or more times, but there was no statistically significant dose–response relationship ($\chi^2 = 1.40$, two-sided $p = 0.24$).

Conclusions — The results, based on a robust study design, show no evidence of an increased risk of developing adult acute leukaemia after topical chloramphenicol use.

KEY WORDS — acute leukaemia; topical chloramphenicol; epidemiology and case–control study

BACKGROUND

Since its introduction in 1948, chloramphenicol has been associated with aplastic anaemia and other blood dyscrasias.[1] Subsequently, acute myeloid leukaemia (AML) was linked to the use of systemic chloramphenicol,[2] and case reports still appear in the literature.[3,4]

Epidemiological studies investigating the relationship between chloramphenicol use and acute leukaemia have produced conflicting results.[5–8] In China, where systemic use of chloramphenicol is widespread (in contrast, to developed countries where the use of chloramphenicol is predominantly topical), an increased risk of acute leukaemia was apparent in children,[5] but not in adults.[6] No increased risk was seen in a study based in the United States (US)[7] whereas in an Italian study[8] an increased risk was only apparent in users of high doses of chloramphenicol.

Much attention has been devoted to the possible risk associated with topical chloramphenicol[9] as it is widely used and because of reports of blood dycrasias after the use of chloramphenicol eye preparations.[10,11] Therefore, a well-designed, large case–control study of acute leukaemia was undertaken to clarify, amongst other issues, the possible role of topical chloramphenicol in the development of acute leukaemia.

METHODS

The design of the study has been described in detail elsewhere.[12] In brief, it is a matched case–control

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study of adult acute leukaemia, which collected cases from 1 April 1991 to the 31 December 1996 in the then English regional health authorities of South West, Wessex and Yorkshire and the counties of Lancashire and Cumbria. Cases were all patients newly diagnosed with acute leukaemia during the study period, aged between 16 and 69 years old and normally resident in the study area. Two controls per case were selected, individually matched to the case by sex, year of birth, ethnic origin and region of residence at diagnosis. The controls were randomly selected from the case's general practitioner (GP) practice list. Participating subjects were interviewed in person using a highly structured questionnaire.

An indicator of deprivation (Townsend Score) was assigned to each subject based on their address at diagnosis for the cases, or for the controls, their address at the date of diagnosis for their matched case (date of pseudo-diagnosis). Townsend Scores[13] were calculated for each enumeration district (ED) (a census small area, containing on average 170 households) in England and Wales using data from the 1991 United Kingdom (UK) census. The resulting continuous scores were then categorized into percentiles allowing each ED in England and Wales to be assigned a deprivation category. For each subject's address at diagnosis, the postcode was validated against the Post Office Postcode Address File using Quick Address™ (v.2.00) and matched to its corresponding ED via the PC2ED program available from Manchester University (MIMAS). This allowed each subject to be assigned a deprivation category.

Data and drug use

In the UK, chloramphenicol is available only on prescription from a medical practitioner; its use should therefore, be recorded in an individual's medical records. Medical records are held by a patient's GP and follow the patient should they change doctors and this has been the case since 1948 when the National Health Service was founded. The records are cumulative and they contain information regarding visits to the GP, hospital admissions and therapy.

To obtain information on the previous use of topical chloramphenicol, the GP records of all cases and controls were perused. For every prescribed dose of chloramphenicol, the date of prescription and number of prescriptions was noted. Chloramphenicol use was recorded from when an individual case's record began to the date of diagnosis of acute leukaemia. The controls had information on chloramphenicol use recorded from the start date of their matched case's record and up to the date of diagnosis of acute leukaemia for their matched case.

Subjects

Of the 807 Caucasian cases and 1593 matched Caucasian controls (21 cases had only one control) that were interviewed, nearly all subjects (99%) had their records abstracted and cases were included in the analysis if their records had been abstracted ($n = 797$). Controls were only to be included in the analysis if their records had been abstracted and if their matched case record had also been abstracted ($n = 1570$). Therefore, there were a total of 2367 subjects included in the analysis (24 cases had one matched control with an abstracted record).

Analysis

Odds ratios and 95% confidence intervals for matched analyses were calculated using conditional logistic regression.[14] A 1-year lag period was implemented to exclude the possibility that chloramphenicol use in the year prior to diagnosis was related to the early symptoms of acute leukaemia. Separate analyses were conducted for acute myeloid leukaemia (AML), acute lymphoblastic leukaemia (ALL) and sex.

Chloramphenicol use was categorized as never (no prescriptions), one to two, or three or more prescriptions. These categories were devised using the median number of prescriptions in the control group. Tests for trend were conducted using the likelihood ratio test and the lowest exposure category (no prescriptions) was defined as the reference category.

All analyses were performed using Stata.[15]

RESULTS

The mean age of the cases and controls was 48.15 years (standard deviation 14.89 years), 57% of cases were male and 86% of cases had AML (Table 1). The mean number of years of information available in the medical records was 29.92 years (standard deviation 11.10 years) for the cases compared with 25.14 years (standard deviation 10.54 years) for the controls.

Table 1 — Number of Caucasian cases and controls with an abstracted medical record by diagnosis, years of information in records and deprivation category

Variable	Cases		Controls	
	n	(%)	*n*	(%)
Total	797	(100)	1570	(100)
Diagnosis*				
AML	686	(86)	–	
ALL	100	(13)	–	
Other	11	(1)	–	
Years of information abstracted from medical records†				
0–9	36	(4)	131	(8)
10–19	119	(15)	342	(22)
20–29	230	(29)	555	(35)
30+	412	(52)	541	(34)
Unknown	0	(0)	1	(0)
Deprivation category‡				
1 (least deprived)	134	(17)	326	(21)
2	140	(18)	285	(18)
3	135	(17)	280	(18)
4	111	(14)	220	(14)
5	108	(14)	197	(13)
6	90	(11)	158	(10)
7 (most deprived)	76	(9)	96	(6)
Unknown	3	(0)	8	(0)

* AML, acute myeloid leukaemia; ALL, acute lymphoblastic leukaemia; other acute leukaemias include four cases of acute biphenotypic leukaemia.
† Number of years of information available in the records; the cases had more years of information available compared to their matched controls ($\chi^2 = 69.43$, two-sided $p < 0.0001$).
‡ Deprivation was coded using categories of the Townsend Score for England and Wales; cases were more likely to live in a deprived area than their matched control ($\chi^2 = 14.28$, two-sided $p = 0.03$).

Due to the discrepancy in the mean number of years of information available for the cases and controls ($\chi^2 = 69.43$, two-sided $p < 0.0001$), this was adjusted for in the analysis. The deprivation category was also adjusted for as the cases were more likely to live in a deprived area than their matched controls ($\chi^2 = 14.28$, two-sided $p = 0.03$). However, adjustment by deprivation category did not change the magnitude of any of the odds ratios.

Table 2 shows the number of cases and controls by prior topical chloramphenicol use with a 1-year lag period. For all acute leukaemia patients no increased risk from chloramphenicol was evident (odds ratio (OR) = 0.91, 95% confidence interval (CI) 0.70–1.17). No increased risk was also apparent in the separate analyses on diagnostic groups or sex: AML (OR = 0.89, 95% CI 0.67–1.18), ALL (OR = 1.14, 95% CI 0.57–2.31), males (OR = 0.98, 95% CI 0.67–1.43) and females (OR = 0.87, 95% CI 0.60–1.25).

Table 3 shows there was a small increased risk for more than three prescriptions, but this did not reach statistical significance (OR = 1.21, 95% CI 0.65–2.25) and there was no significant dose–reponse relationship ($\chi^2 = 1.40$, two-sided $p = 0.24$).

DISCUSSION

This large robustly designed epidemiological study, which collected data from past medical records, failed to show an increased risk of acute leukaemia following topical chloramphenicol use. This is the only epidemiological study to investigate whether or not there is an association exclusively between topical chloramphenicol and acute leukaemia. However, it is consistent with other case–control studies, which have investigated systemic chloramphenicol use and the subsequent risk of leukaemia in adults.

A study of adult leukaemia in Shanghai[6] (317 cases of acute leukaemia) found no increased risk of acute leukaemia (ALL OR = 0.8 95% CI 0.4–1.5; AML OR = 0.7 95% CI 0.4–1.1). However, chloramphenicol use was ascertained only at interview with the subject, or a surrogate, rather than from medical records and therefore, the study could be subject to differential recall bias. Doody *et al.*[7] found no increased risk of AML (113 cases, OR = 0.4, 95% CI 0.1–1.5). Traversa *et al.*[8] (202 cases) only found an increased risk for high users (defined as duration of use greater than the median in the control group) of chloramphenicol/thiamphenicol (OR = 1.8, 95% CI 0.6–5.3). This result did not reach statistical significance and also drug use was only collected for a relatively short period of time (30 to 48 months prior to the date of diagnosis of acute leukaemia), which may not be a long enough time period to assess risk accurately.

In this study a small increased risk (OR = 1.21 95% CI = 0.65–2.25) was observed if chloramphenicol was prescribed three, or more times. The dose and duration of chloramphenicol use was not recorded and therefore, the dose–response analysis may not be adequate to assess risk. Nevertheless there was no statistically significant dose–

Table 2 — Number of cases and controls, adjusted odds ratio (OR)* and 95% confidence intervals (CI) for topical chloramphenicol status with 1-year lag period

Variable		Case *n*	Control *n*	OR*	95% CI
Total		797	1570		
	Never	602	1186		
	Ever	195	384	0.91	0.70–1.17
Diagnosis group†					
AML	Never	521	1028		
	Ever	165	325	0.89	0.67–1.18
ALL	Never	73	142		
	Ever	27	54	1.14	0.57–2.31
Sex					
Male	Never	355	697		
	Ever	98	194	0.98	0.67–1.43
Female	Never	247	489		
	Ever	97	190	0.87	0.60–1.25

* Odds ratio adjusted for number of years of information available in General Practitioner Records and Deprivation Category.
† AML, acute myeloid leukaemia; ALL, acute lymphoblastic leukaemia.

Table 3 — Number of cases and controls, adjusted odds ratio* (OR) and 95% confidence intervals (CI) for number of prescriptions for topical chloramphenicol status with 1-year lag period

Number of prescriptions	Case	Control	OR*	95% CI
0	602	1186	1.00	
1–2	163	343	0.87	0.67–1.13
⩾3	32	41	1.21	0.65–2.25

* Odds ratio adjusted for number of years of information available in General Practitioner Records and Deprivation Category. Test for trend with lowest exposure category (0 prescriptions) as baseline ($\chi^2 = 1.40$, two-sided $p = 0.24$).

response relationship ($\chi^2 = 1.40$, two-sided $p = 0.24$).

As early as the mid-1950s, the use of systemic chloramphenicol in the UK has only been indicated for a limited number of life-threatening conditions (including typhoid fever, *Haemophilus influenza* meningitis) due to the risk of bone marrow toxicity.[16] Accordingly, in this study we found only three subjects who had ever been prescribed oral chloramphenicol (one case, and two controls) which occurred during the late 1950s and early 1960s. Therefore, it was not possible to assess the risk of acute leukaemia by systemic chloramphenicol use.

A number of methodological issues need to be considered. As with all studies which abstract information on drug use from medical records, the actual compliance of the patient is unknown. Did the patient collect the prescription and if so, was the course completed? In order to partly address this problem, every subject in the study was asked at interview if they had ever used eye-drops prescribed either by their GP, or by a hospital doctor. This gives some indication of chloramphenicol use, as it is the most common eye-drop preparation prescribed in the UK[17] and is available only on prescription. Reassuringly no increased risk was evident for self-reported eye-drop use (OR = 0.99 95% CI 0.80–1.22) and these data produced a similar odds ratio to the one found using the data from the GP records (OR = 0.91 95% CI 0.70–1.17).

It is recognized that bone marrow toxicity can follow systemic administration of chloramphenicol either by a rare irreversible idiosyncratic reaction, or by a generally reversible bone marrow suppression, which occurs in a dose-dependent manner. However, it is questionable whether systemic toxicity can occur after topical use. It has been suggested that following topical eye administration systemic absorption may occur via the nasolacrimal duct.[18] However, two studies, which have investigated systemic absorption[18,19] after topical chloramphenicol therapy, failed to observe any accumulation of chloramphenicol at a detectable level in the patient's sera. This suggests that topical chloramphenicol poses no risk of toxicity to the

KEY POINTS

- There is no evidence of an increased risk of developing adult acute leukaemia after topical chloramphenicol use.
- Past topical chloramphenicol use was ascertained from medical records.
- This is a large, well-designed study and the only epidemiological study which has evaluated the risk of acute leukaemia and topical chloramphenicol use.

bone marrow and therefore, presumably no subsequent risk of developing acute leukaemia.

To the authors' knowledge, this is the only epidemiological study, which has investigated the use of topical chloramphenicol and its possible role in the development of adult acute leukaemia. This is a pertinent question in the UK as chloramphenicol is often the first choice antibiotic in treating eye infections[20] due to its broad spectrum of activity, low incidence of local sensitivity reactions and relative low cost. In conclusion, there appears to be no evidence of an association between topical chloramphenicol use and the development of acute leukaemia. Restriction of the use of topical preparations of chloramphenicol on the grounds of a risk of acute leukaemia would not appear to be justified.

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