Health Effects of Patients Given Methoxyflurane in the Pre-Hospital Setting: A Data Linkage Study

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Abstract: *Background*: Methoxyflurane administered *via* an inhaler is a common analgesic agent used by ambulance services in Australia; however little published data exists as to its efficacy or effectiveness in this setting. There have been several reports that have suggested that the use of Methoxyflurane may be associated with the occurrence of hepatitis and renal disease. Such concerns have led to an increasing reluctance to use Methoxyflurane as an analgesic agent in the pre-hospital setting. The aim of this study was to determine whether the event rates of heart disease, renal disease, hepatic disease, diabetes or cancer in patients who received Methoxyflurane compared with those not receiving Methoxyflurane pre-hospital.

Methods: Routinely collected administrative data for ambulance, emergency department, hospital morbidity and mortality were linked by using probabilistic matching to establish a cohort of patients managed by the ambulance service in Western Australia. The cohort covered a period of 10 years (1990 – 2000) with follow-up until 2004 allowing for a minimum of four and maximum of 14 years follow-up. Primary outcome was defined as a composite end point of any record indicating either hospital admission or death for the diseases under investigation. Event rates were age standardised and odd ratios plus 95% confidence intervals were to determine risk estimates.

Results: Total 135,770 patients were entered into the study of which 17, 629 (13%) had received Methoxyflurane. There were 14, 410 (81.7%) patients, where Methoxyflurane was administered only once with one patient receiving Methoxyflurane on 27 occasions. Trauma was the most common indication for Methoxyflurane being administered to 9, 755 (55.3%) patients. The odd ratios for each of the five disease groups under investigation ranged from 0.87 to 1.06 with the 95% confidence interval for each estimate including 1.0.

Conclusion: There was no difference observed in event rates for heart disease, renal disease, hepatic disease, diabetes or cancer in patients who received Methoxyflurane in the pre-hospital setting as compared with those not receiving Methoxyflurane.

Keywords: Methoxyflurane, Analgesia, Emergency Medical Service, Record Linkage.

INTRODUCTION

Published reports of Methoxyflurane dating back to the 1960's identify its use initially as an anaesthetic agent than more recently as a analgesic for use in the pre-hospital setting [1-6]. While Methoxyflurane – a halogenated ether - has been used as an analgesic by numerous ambulance services in Australia for over two decades, very few clinical data describing its efficacy, effectiveness and safety currently exists. Recent Australian studies have demonstrated that in children, Methoxyflurane appears to be an effective analgesic with a very low side effect profile [7, 8].

In the late 1980s, there were a number of published reports indicating that the use of Methoxyflurane may potentially be associated with harm [9-13]. This harm was mainly observed when Methoxyflurane was used in obstetrics, where elevated inorganic fluoride levels in mothers and attending staff. In 1983, Delia identified two cases of hepatitis associated with Methoxyflurane when used for obstetric analgesia [10]. More specifically in 1987, Toomath described two cases of renal failure leading to death following administration of Methoxyflurane over a period of 14 and 16 days [9]. Methoxyflurane was subsequently withdrawn in New Zealand. While the clinical and anecdotal evidence would indicate that Methoxyflurane is a useful and effective analgesic agent; its potential renal and hepatic toxicity in particular continue to raise concerns in regards to safety.

The Western Australian Ambulance Service (WAAS) is responsible for providing the ambulance service in the Western Australia and has been using Methoxyflurane as its primary analgesic agent for over two decades. Despite such extensive use, an evaluation of any potential health effects on patients administered Methoxyflurane as a pre-hospital analgesic has not been undertaken.

The Western Australia has considerable expertise in heath record linkage. The Health Information Linkage Branch located at the Western Australian Department of Health undertakes core linkage of statewide Hospital Morbidity Data (HMD), Emergency Department Information System (EDIS) and the Death Register (DR) to which we are able to link ambulance service data. A full description of this linkage system has been previously published [14]. The

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Table 1. ICD 9 and ICD 10 Codes Used to Identify Disease Outcomes

Cardiovascular Disease		
ICD9	Acute Myocardial Infarction	410.0,1,2,3,4,5,6,7,8,9
	Other acute and subacute forms	
	of Ischaemic Heart Diseases	411.0,1,8
	Old Myocardial Infarction	412
	Angina Pectoris	413.0,1,9
	Other forms of chronic	
	Ischaemic Heart Diseases	414.0,1,8,9
ICD10	Angina Pectoris	I20.0,1,8,9
	Acute Myocardial Infarction	I21.0,1,2,3,4,9
	Subsequent Myocardial Infarction	I22.0,1,8,9
	Certain current complications following	
	Acute Myocardial Infarction	I23.0,1,2,3,4,5,6,8
	Other Ischaemic Heart Diseases	I24.0,1,8,9
	Chronic Ischaemic Heart Diseases	I25.0,1,2,3,4,5,6,8,9
Cerebrovascular Disease		
ICD9	Intracerebral Haemorrhage	431
	Occlusion and stenosis of	
	precerebral arteries	433.0,1,2,3,8,9
	Occlusion of cerebral arteries	434.0,1,9
	Acute, but ill-defined,	
	Cerebrovascular Disease	436
ICD10	Cerebral Infarction	I63.0,1,2,3,4,5,6,8,9
	Stroke	I64
	Occlusion and stenosis of	
	precerebral arteries, not resulting	
	in Cerebral Infarction	I65.0,1,2,3,8,9
	Occlusion and stenosis of	
	cerebral arteries, not resulting	
	in Cerebral Infarction	I66.0,1,2,3,4,8,9
	Intracerebral Haemorrhage	
	(haemorrhagic stroke)	I61.0,1,2,3,4,5,6,8,9
Diabetes	in Cerebral Infarction	
ICD9	Diabetes Mellitus	250.0,1,2,3,4,5,6,7,8,9
ICD10	Impaired glucose regulation	E09.0,1,8,9
	Type 1 diabetes mellitus	E10.0,1,2,3,4,5,6,7
	Type 2 diabetes mellitus	E11.0,1,2,3,4,5,6,7
	Other specified diabetes mellitus	E13.0,1,2,3,4,5,6,7
	Unspecified diabetes mellitus	E14.0,1,2,3,4,5,6,7

(Table 1). Contd…..

Cancer		
ICD9	Malignant neoplasm of:	
	-lip, oral cavity,and pharynx	140-149
	-digestive organs and peritoneum	150-159
	-respiratory and intrathoracic organs 1	60-165
	-bone, connective tissue, skin & breast	170-175
	-genitourinary organs	179-189
	-other & unspecified sites	190-199
	-lymphatic & haemopoietic tissue	200-208
ICD10	Neoplasm	C01-C96
	In-situ Neoplasms	D00-D09
	Neoplasms of uncertain or	
	unknown behaviour	D37-D48
Renal		
ICD9	Acute glomerulonephritis	580.0,4,8,9
	Nephrotic syndrome	581.0,1,2,3,8,9
	Chronic glomerulonephritis	582.0,1,2,4,8,9
	Nephritis and nephropathy, not	
	specified as acute or chronic	583.0,1,2,4,6,7,8,9
	Acute renal failure	584, 584.5,6,7,8,9
	Chronic renal failure & impairment	585, 585.1,9
	Renal failure, unspecified	586
ICD10	Hypertensive renal disease	I12
	Hypertensive heart & renal disease	I13
	Glomerular disease	N00-N05
	Renal tubulo-interstitial diseases	N10-N12
	Renal failure	N17-N19
Liver Disease		
ICD9	Acute and subacute necrosis of liver	570
	Chronic liver disease & cirrhosis	571.4,5,6,8,9
	Liver abscess & sequelae of	
	Chronic liver disease	572.0,1,2,3,4,8
	Other disorders of liver	573.0,3,4,8,9
ICD10	Toxic liver disease	K71.0,1,2,3,4,5,6,7,8,9
	Hepatic failure,	
	not elsewhere classified	K72.0,1,9
	Chronic hepatitis,	
	not elsewhere classified	K73.0,1,2,8,9
	Fibrosis & cirrhosis of liver	K74.0,1,2,3,4,5,6
	Other inflammatory liver disease	K75.0,1,2,3,4,8,9
	Other diseases of liver	K76.0,1,2,3,4,5,6,7,8,9

quality of the hospital morbidity data linkage has been assessed by a sampling technique to the percentage of invalid links (false positives) and missed links (false negatives) estimated to both be 0.11% [14].

The aim of this study was to use record linkage to compare the morbidity and mortality event rates in patients administered Methoxyflurane in the pre-hospital setting to a cohort of pre-hospital patients who did not receive Methoxyflurane.

METHODS

The Western Australian Ambulance Service provides 100% of all road based emergency ambulance services for WA covering approximately 2.5 million square kilometers. Patient, demographic, service and clinical details are recorded on the patient care record form (PCRF) for all occasions of service. This information is subsequently entered into a name identified by a computerised patient recording system.

A retrospective cohort of patients managed in the pre-hospital setting by the Western Australian Ambulance Service during 1990 to 2004, data was linked to the HMD, EDIS and DR data. Linkage keys were developed by using probabilistic matching of individual patients based on assigned weights to patient identifiers common in the master files. Questionable links were resolved through clerical checks of the data. These record linkage keys allowed for the creation of a unique patient record consisting of the information from each of the linked datasets. Analyses were then undertaken based on individual episodes of care or by individual patients (i.e. all episodes of care relating to that specific patient).

The cohort of patients receiving Methoxyflurane administration was identified through a specific code noted on PCRF, which is recorded in the ambulance service database. Index cases were determined as the first recorded pre-hospital episode, where the patient received Methoxyflurane. Where patients used an ambulance subsequent to the index event and Methoxyflurane was again administered, these events were summed to give an aggregated number of Methoxyflurane events over the study period. The non Methoxyflurane administered cohort consisted of all patients managed by the ambulance service but did not receive Methoxyflurane during the study period.

Methoxyflurane (0.3%) is administered under a clinical practice guideline allowing for 3mls *via* inhaler to be given which may be repeated once. It was not possible to determine the exact dose administered during any one episode.

A composite outcome of either hospital admission or death was used as the primary endpoint. These were identified from the ICD9 or ICD10 diagnostic code relating to either "any ischaemic heart disease", "any diabetes", "any cancer", "any renal disease" or "any hepatic" disease recorded in either the HMD and /or DR. Where multiple diseases were recorded for a patient, these were included as separate occurrences. Table **1** outlines the ICD9 and ICD10 codes used in the study.

The cohort consisted of all patients transported by ambulance to hospital between 1990 and 2000 with follow-up period extending to the 31st December 2004. This was allowed for a minimum of 4 years and a maximum of 14 years of follow-up.

Univariate and descriptive analysis was undertaken to describe the cohort. Crude and age standardized event rates were calculated for the primary outcome for the Methoxyflurane and non Methoxyflurane groups. Denominators for age strata were obtained from the Australian Bureau of Statistics and standardisation was calculated by using direct method. Logistic regression was used to calculate the odd ratios for each outcome of interest. In each of the models developed age and gender were included as these were considered potential confounders for outcome, with 95% confidence intervals derived for each of the estimates. Analysis was undertaken by using SPSS version 15. Ethics approval for the study was granted by the Human Research Ethics Committees at the University of Western Australia and Health Department of Western Australia.

RESULTS

The cohort comprised 135,770 patients of which 17,629 (13%) received at least one dose of Methoxyflurane. The average age in the Methoxyflurane group was 45.8 years (Median 42.0 years; Range 1 – 104 years) compared to 43.4 (Median 42.0 years; Range 1 – 102 years) in the non Methoxyflurane group. Males accounted for 48.9% and 51.1% of the Methoxyflurane and non-Methoxyflurane groups, respectively.

Among 17,629 patients who received Methoxyflurane, 14,410 (81.7%) patients received Methoxyflurane on a single occasion. 1,575 (8.9%) received Methoxyflurane on two separate occasions with a further 341 (2.0%) receiving Methoxyflurane on 3 separate occasions. Only one patient received Methoxyflurane on 27 separate occasions.

Trauma was the primary indication for the use of Methoxyflurane in 9,755 (55.3%) cases with acute abdominal pain 2, 207 (12.5%), inflammatory musculoskeletal 2,109 (12.0%), cardiac 479 (2.7%) and renal colic 247 (1.4%) cases. These five conditions comprised a total of 83.9% of all Methoxyflurane administrations.

In patients administered Methoxyflurane, no increased risk was observed in any of the disease groups under investigation when compared with pre-hospital care patients who were not administered Methoxyflurane. In addition the time taken for the first occurrence of disease to occur was similar to the Methoxyflurane and non Methoxyflurane groups. These results are further described in Table **2**. Furthermore, we observed no increased risk of disease occurrence in the Methoxyflurane group for each individual ICD code within each of the five disease categories investigated.

Additional analysis was undertaken on a subgroup of cases comprising children aged less than or equal to 12 years of age. This sub-cohort comprised 14,753 patients of which only 594 (4%) received Methoxyflurane. As with the over 12 years of age cohort no increased risk of disease was observed (Table **3**).

DISCUSSION

Within the Western Australia, Methoxyflurane has been used by the ambulance service as an analgesic agent for over two decades. It is patient self administered *via* an inhaler and

Table 2. Outcomes by Disease Group for Patients Receiving and Not Receiving Methoxyflurane Pre-Hospital

	Ischaemic Heart Disease	**Diabetes**	**Renal Disease**	**Cancer**	**Hepatic Disease**
All events n	25688	16476	12445	24065	2718
Received Methoxyflurane					
N (%)	2271 (8.8)	1916 (11.6)	1596 (12.8)	2898 (12.0)	373 (13.7)
Age Mean (Median)	69.2 (72.0)	61.5 (65)	66.4 (73.0)	67.7 (72.0)	52.7 (51.5)
Male n (%)	1257 (45.4)	837 (43.7)	645 (40.4)	1273 (43.9)	165 (44.2)
Number of administrations Mean (median; range)	1.3 (1.0; 1-24)	1.3 (1.0; 1-19)	1.3 (1.0; 1-11)	1.3 (1.0; 1-12)	1.6 (1.0; 1-27)
Time to onset of event (yrs) Mean (median)	2.8 (1.8)	2.7 (1.4)	4.1 (3.7)	4.0 (3.4)	3.9 (3.5)
Crude event rate (per 1,000 patients)	1.57	1.09	0.91	1.64	0.21
Age standardised event rate (per 1,000 patients)	1.21	1.11	0.93	1.59	0.22
No Methoxyflurane					
N	23417	14560	10849	21167	2345
Age Mean (Median)	67.0 (69.0)	60.7 (64.0)	65.7 (71.0)	66.4 (70.0)	55.8 (57.0)
Male n (%)	12927 (55.2)	7407 (50.9)	5603 (51.6)	11172 (58.2)	1291 (54.8)
Time to onset of event (yrs) Mean (median)	3.2 (1.9)	3.7 (2.6)	5.8 (5.5)	5.2 (4.7)	5.1 (4.4)
Crude event rate (per 1,000 patients)	1.98	1.23	0.92	1.79	0.19
Age standardised event rate (per 1,000 patients)	1.48	1.21	0.91	1.68	0.20
Odds ratio (age adjusted) (95% CIs)	0.95 0.72 to 1.23	0.87 0.63 to 1.34	0.98 0.93 to 1.04	0.90 0.86 to 1.01	1.06 0.95 to 1.19

Table 3. Outcomes by Disease Group for Paediatric Patients Receiving and Not Receiving Methoxyflurane Pre-Hospital

	IHD	Diabetic	Renal	Cancer	Hepatic
Received Methoxyflurane					
N	1	6	2	3	2
Crude event rate (per 1,000 patients)	1.6	10.1	3.3	5.0	3.3
No Methoxyflurane					
N	14	153	141	134	28
Crude event rate (per 1,000 patients)	0.9	10.8	9.9	9.4	1.9
Odds ratio 95% CIs	1.7 (0.2 to 12.7)	0.9 (0.4 to 2.1)	0.3 (0.1 to 2.3)	0.5 (0.1 to 1.6)	1.7 (0.4 to 7.2)

indicated for the temporary emergency management of acute pain in the pre-hospital setting. There have been a small number of published studies describing the efficacy, effectiveness and safety of this agent. The limited data available indicates that Methoxyflurane is an effective analgesia; however an adverse association between the occurrence of hepatitis and renal disease in patients being administered or by using Methoxyflurane has been reported. In each of these reports, Methoxyflurane was used in higher concentrations and / or for extend period of time than what is used by the ambulance service as a pre-hospital analgesic.

This population-based study used routinely collected linked administrative data to assemble a large cohort of patients over a 14 year period. The patients followed-up for at least 4 years and to a maximum of 14 years. The cohort consisted of 135,770 cases with 17,629 (13%) receiving Methoxyflurane.

The sex and age characteristics were generally similar in each of the disease groups for both Methoxyflurane and non-Methoxyflurane patients. In this study, over 80% of the patients who received Methoxyflurane received this agent on a single occasion. It was observed that the time to event was generally similar between the two groups; however, a trend towards a shorter period in the Methoxyflurane group compared to the non-Methoxyflurane group was noted. This may be due to the underlying nature and severity of the disease in patients with more advanced disease states and requiring analgesia.

In each of the five disease conditions investigated the crude and age adjusted event rates were similar in the Methoxyflurane group compared with the non Methoxyflurane group. Odds ratios for the occurrence of disease or death from disease in those who received Methoxyflurane compared to those who were non significant with the 95% confidence limits including an odd ratio of 1.0. These findings remained similar for both the whole cohort and in the cohort of children aged 12 years or less.

This is the first study, which has attempted to establish whether long-term health may occur in patients administered Methoxyflurane. The study has not identified any increase in the risk of disease occurrence or death with the use of Methoxyflurane to that of a similarly comparable group.

The findings of this study are at odds with the previously published reports of adverse health outcomes, leading to death in some cases. It is important when considering these findings where adverse health events that occurred, Methoxyflurane was used in both higher concentrations and over a longer period of time in order to manage acute pain in these patients. Similarly, the cumulative effects of Methoxyflurane producing toxicity after prolonged exposure may explain such findings. In the Western Australian Ambulance Service, the exposure to Methoxyflurane was predominantly a one off event, of a lower concentration and given over a relatively short duration of usually less than 45 minutes.

Despite this being, a large population based study, a number of limitations associated with the use of administrative data should be highlighted. We were not able to ascertain the accuracy / validity of the data for each database used. However, previously published validation studies of clinical cohorts assembled through administrative databases have indentified error rates of less than 5%. Similarly, the influence of any data inaccuracies contained in this clinical cohort of ambulance patients – receiving or not receiving Methoxyflurane - is likely to have minimal effect on the outcomes observed. In addition, we were not able to include those patients who may have developed the disease under investigation but were not admitted to hospital or died. However the likelihood of patients developing such diseases and not having at least one hospital admission (particularly in the Western Australia) would be very low and thus would have minimal impact on our findings.

A further limitation of this study is that we were not able to assess the actual dose of Methoxyflurane administered to patients during the course of their pre-hospital care. Similarly, we are not able to determine or model a dose – response relationship for individual patients receiving Methoxyflurane. Finally this study focussed on the exposure of patients to mostly one off or very infrequent doses of Methoxyflurane. The health effects associated with occupational exposure of Paramedics to Methoxyflurane could not be assessed and may have a different risk profile.

Notwithstanding the above, this study suggests that there is no evidence, that the use of Methoxyflurane in the pre-hospital setting as currently recommended, is associated with an increased likelihood of the Ischaemic Heart Disease, Diabetes, Cancer, Renal or Hepatic disease in patient's receiving this agent.

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CONFLICTS OF INTEREST

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