

Original article

Psychotropic drugs use and risk of heat-related hospitalisation

Karin Martin-Latry^{a,b,c,*}, Marie-Pierre Goumy^d, Philippe Latry^e, Claude Gabinski^d,
Bernard Bégaud^{a,b,c}, Isabelle Faure^d, Hélène Verdoux^{a,c}

^a Université Victor Segalen Bordeaux 2, France

^b Département de Pharmacologie, CHU Bordeaux, France

^c Inserm U657, Bordeaux, France

^d Service des urgences-réanimation, Centre Hospitalo-Universitaire de Saint-André, Bordeaux, France

^e Direction Régionale du Service Médical de l'Assurance Maladie d'Aquitaine, CNAM-TS, France

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Abstract

Objective. — To assess if use of psychotropic drugs is associated with an increased risk of admission for heat-related pathologies during a heat wave period.

Method. — We conducted a matched case–control study. Cases were defined as subjects admitted to an emergency department for heat-related pathology (hyperthermia or heat stroke) over the August 2003 heat wave. Controls were defined as subjects living in the same area but not hospitalised over the same period and who had at least one prescription form submitted for refunding by the social security insurance in July 2003. Multivariate analyses were used to identify psychotropic drugs independently associated with hospital referral during the heat wave period.

Results. — Out of the 1405 patients admitted to the emergency department, 56 (4%) presented with heat-related pathology. The mean age of cases was 83 years. Multivariate analyses showed that cases were more likely than controls to be treated with anticholinergic drugs (OR 6.0, 95% CI 1.8–19.6), antipsychotics (OR 4.6, 95% CI 1.9–11.2) or anxiolytics (OR 2.4, 95% CI 1.3–4.4).

Conclusion. — In special risk situations such as heat waves, the risk/benefit ratio of psychotropic drugs which could interfere with body temperature regulation has to be carefully assessed, particularly in the elderly.

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Keywords: Heat wave; Psychotropic medication; Old age

1. Introduction

Over the last decades, several heat waves have occurred all over the world [16,17,20,22]. In August 2003, most European countries were confronted with an unprecedented heat wave [6,12]. The death rate increase was especially marked in France [15,26], resulting in nearly 15,000 excess deaths [7,25]. Heat waves may have a direct impact on health by inducing a failure

in thermoregulation mechanisms [4]. A heat exhaustion–dehydration syndrome occurs when high ambient temperature exceeds thermolysis capacity. Heat stroke, the most severe complication of exposure to high ambient temperature, is characterised by a core body temperature above 40 °C associated with central nervous system symptoms (delirium, convulsion, coma). This state can lead to a multiorgan dysfunction, partly due to the cytotoxic effects of heat and the associated inflammatory response, with acute renal, respiratory or circulatory failures, and haemorrhagic complications. The mortality rate of heat stroke is around 50% [4].

Risk factors for hospital admission related to health consequences of heat wave most frequently reported in the literature

* Corresponding author. Inserm U657, Département de Pharmacologie, Université Victor Segalen, 146 rue Léo Saignat, 33 076 Bordeaux cedex, France. Tel: +33 557 571 561; fax: +33 557 574 660.

E-mail address: karin.latry@pharmaco.u-bordeaux2.fr (K. Martin-Latry).

are old age, presence of comorbidities, social isolation, poverty and absence of air-conditioning [9,10,17,19,22,23]. Mortality rates are higher in women [5,7,20] and in elderly subjects (>65 years) [10,18,27]. Thermoregulation is impaired in elderly subjects even when healthy [3]. They present with elevated sweating thresholds and with a reduced perception of thirst. Furthermore, they notice increase in skin temperature only when it is higher than 5 °C, while this threshold is 0.5 °C in young adults. Hence, they are less likely than young adults to adjust their behaviour during heat wave periods. Higher mortality rates in women were found only in European countries, and might be related to a lower sweating response to heat in women compared to men.

High ambient temperature may also have indirect health consequences by worsening pre-existing medical conditions such as heart or respiratory diseases, since cardiovascular or respiratory systems are confronted with a major stress during heat wave periods [3]. Some subjects may be at higher risk of presenting health problems during heat wave periods because of a pre-existing medical condition, but also because of the treatment prescribed for this disease. For example, diuretics prescribed for heart disease could worsen the heat wave effect by provoking dehydration and electrolytic disorders. Similar mechanisms may be implicated in the increased mortality rates found in subjects with psychiatric disorders [2,9,11,17,23]. Due to their pharmacological properties, several psychotropic drugs could interfere with temperature regulation [1,13]. Antipsychotics, serotonergics, antihistamine and anticholinergic drugs can reduce heat elimination via the parasympathic pathway. Antipsychotics and serotonergic drugs could also directly induce hyperthermia. The pharmacokinetics of some drugs such as lithium or antiepileptic drugs could be altered by dehydration.

The aim of the study was to assess if use of psychotropic drugs was associated with an increased risk of admission for heat-related pathologies in an emergency department during a heat wave period.

2. Subjects and methods

We conducted a matched case–control study. Cases were defined as subjects admitted to the emergency department of Saint André University Hospital (Bordeaux, Aquitaine region, France) with a hospital diagnosis of heat-related pathology over the period 1–20 August 2003. Cases were identified using a systematic review of clinical charts of all subjects admitted in the department over the period of the study. Two heat-related pathologies were considered: (i) heat stroke, defined as body core temperature above 40.6 °C (105.1 °F) with central nervous system symptoms [21]; (ii) hyperthermia, defined as body core temperature above 38.3 °C (100.9 °F) without identified aetiology (infection or other); the 38.3 °C criteria was that used and recorded in the medical charts by the physicians of the emergency department to discriminate subjects with and without hyperthermia. Diagnoses of hyperthermia were taken into account in order to include all potential cases of heat-related conditions since the distinction between heat stroke

and hyperthermia was often difficult in the emergency setting. Indeed, temperature at admission did not always reflect the medical condition since treatment aimed at reducing body temperature was frequently started before admission.

Information on treatments at admission was collected in the clinical charts. Only names of drugs were collected since information on dosage was often lacking or unreliable. Drugs were classified according to Anatomical Therapeutic Classification (ATC) code. Patients were considered as exposed if having taken at least one drug acting on the central nervous system susceptible to interfere with heat regulation or to worsen an exhaustion/dehydration syndrome. These drugs were selected according to the list published by the French Health Ministry after the 2003 heat wave [1] which included the following products: antidepressants, antiepileptics, anticholinergics, anxiolytics, hypnotics antipsychotics and cholinesterase inhibitors.

Controls were randomly extracted from the Social Security Insurance (SSI) database of Aquitaine region. This computerized database encompasses approximately 80% of the general population and includes information on patients' demographic characteristics, prescribers and refunded prescribed drugs. No information on diagnosis or on demographic characteristics is available in this database, hence matching on pre-existing illness or socio-economic status was not possible. Controls were defined according to the following criteria: (i) subjects living in the same area as cases, hence having a similar probability to be admitted to the same hospital if they had presented with heat-related diseases; (ii) not hospitalised over the heat wave period; (iii) with at least one prescription form submitted for refunding by the SSI during July 2003. Information on treatment over the period of interest was that given in the prescription form. We used an exposure time-window of one month before the index date (1 August 2003) to categorise a subject as exposed to a drug over the heat wave period. Cases and controls (20 per cases) were matched for gender and age (year of birth, except for subjects aged 94 and 97 for whom not enough controls born the same year were available, and who were matched ± 2 –3 years).

3. Statistical analyses

Analyses were done using STATA [24]. The independent variable was admission over the heat wave period, and the dependent variable was exposure to psychotropic drugs. First, the strength of the association between hospitalisation and each class of drugs was measured by an odds ratio (OR) using conditional univariate logistic regression taking into account matching. The level of statistical significance was set at 0.05 and the statistical uncertainty of the estimates was assessed by 95% confidence intervals (95% CI). Then variables with a level of statistical significance <0.05 were included in a matched multivariate logistic regression model. Use of anticholinesterase inhibitors (anti-Alzheimer drugs) was forced in the model as a proxy for Alzheimer disease, since this condition may confound the association between psychotropic use and increased risk of heat related pathologies due to limited

ability to adjust water input. The final model was determined using a backward stepwise procedure, with 0.05 as the threshold for eviction from the model.

4. Results

4.1. Characteristics of the sample

Over the study period, 1405 patients were admitted to the emergency department. Among them, 56 (4%) presented with heat-related pathologies. Nearly two out of three cases were females ($n = 35$, 62.5%), their mean age of was 83 years (range 64–97) and 32% were aged 90 years and over. The mortality rate during the stay in the emergency department was 42.9% ($n = 24$), among them 66.7% were women. Most deaths (87.5%) occurred within 24 h after admission.

The daily numbers of admission and deaths, and the air temperatures over the study period are shown in Fig. 1. The heat peak wave occurred from 4 to 13 August, where the day and night temperatures remained higher than 35 °C (95 °F) and 20 °C (68 °F), respectively. The heat peak wave spanned 5 days (8–13 August) with maximum temperatures over 36 °C (96.8 °F) and minimum temperatures from 21.2 °C (70.2 °F) to 22.9 °C (73.2 °F). More than three out of four (80.4%) of the heat-related patients were admitted over this 5-day period. No statistical test was performed to explore the association between temperatures and daily number of admissions since the number of cases was too low.

4.2. Drug exposure and heat-related diseases

Most patients with heat-related pathologies ($n = 47$, 83.9%) used at least one drug. As a consequence of the study design, all controls used at least one drug. A high proportion of cases used psychotropic drugs: nearly 40% of them used anxiolytics and nearly one-third used antidepressants (Table 1). In univariate analyses, use of all types of central nervous system drugs, except hypnotics and selective serotonin reuptake inhibitors, was significantly associated with admission for heat-related pathologies (Table 1). Multivariate analyses showed that drugs independently associated with admission were anticholinergic

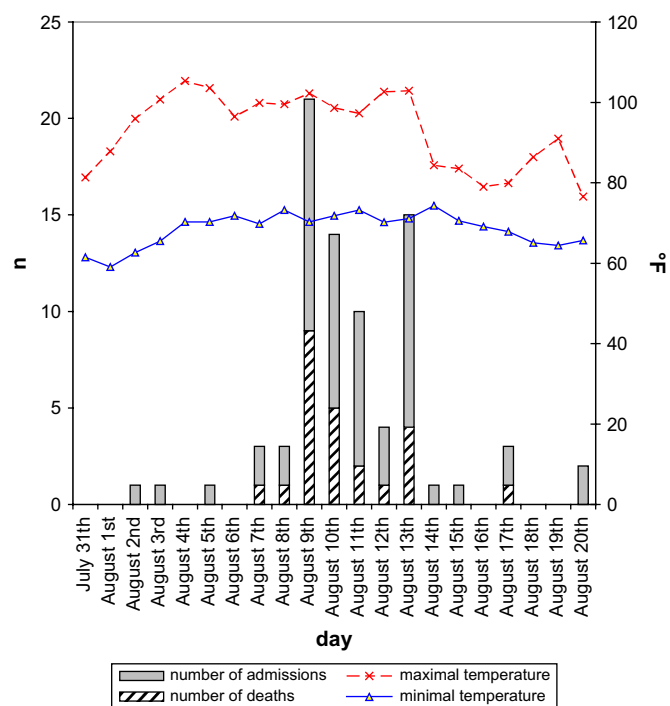


Figure 1. Number of daily heat admissions and deaths according to minimum and maximum air temperatures.

drugs (OR 6.0, 95%CI 1.8–19.6), antipsychotics (OR 4.6, 95%CI 1.9–11.2), and anxiolytic drugs (OR 2.4, 95%CI 1.3–4.4).

5. Discussion

Anticholinergic drugs, antipsychotics and anxiolytic drugs were found to be independent risk factors for hospitalisation for heat-related pathologies during heat wave. These findings are consistent with the known pharmacological effects of these drugs [1,13]. Use of anticholinergic drugs can disturb thermoregulation via inhibition of the parasympathicomimetically mediated sweat secretion, sweating inhibition reducing heat elimination. The set point of the temperature regulation centre can be increased by the antidopaminergic activity of

Table 1

Associations between psychotropic drug exposure and heat-related pathologies explored using univariate analyses

	Cases: subjects admitted for heat-related diseases		Controls: subjects not admitted over the heat-wave period		OR	95% CI ^a
	n	%	n	%		
Anxiolytics	22	39.3	189	16.9	3.2	1.8–5.6 ^b
Hypnotics	7	12.5	139	12.4	1	0.4–2.3
Antidepressants	17	30.4	122	10.9	3.6	2–6.5 ^b
Tricyclics	3	5.4	14	1.3	4.5	1.3–16 ^b
SSRIs ^c	6	10.7	81	7.2	1.5	0.6–3.7
Antiepileptics	4	7.1	22	2.0	3.8	1.3–11.5 ^b
Antipsychotics	11	19.6	24	2.1	11.1	5.2–24.2 ^b
Anticholinergics	7	12.5	11	1.0	14.2	5.2–38.3 ^b
Cholinesterase inhibitors	5	8.9	23	2.05	4.7	1.7–12.8 ^b

^a Odds ratio 95% confidence interval.

^b Significant association.

^c Selective serotonin reuptake inhibitors.

antipsychotics. Anxiolytics and antipsychotics may modify the vigilance level and hence alter behaviour regulating temperature and water intake.

A link between maximal and especially minimal temperatures and excess hospital admission rate has been previously reported [14,18]. In accordance with our findings, a case–control study on the consequences of the heat wave in St Louis and Kansas City in 1980, found that use of antipsychotics (phenothiazines, butyrophenones, or thioxanthenes) was associated with increased risk of fatal heatstroke [8]. Studies on heat waves occurring in Chicago [23] also reported that psychiatric illness was associated with an increased risk of heat condition or heat-related deaths.

These findings have to be interpreted in the light of potential limitations. Since no information was available on the motives for prescription, it was not possible to assess if the heat-related conditions were induced by the drugs or by the psychiatric conditions for which these drugs were prescribed. For example, subjects treated by antipsychotics may be at higher risk of presenting with heat-related diseases due to the impact of these drugs on thermoregulation or on behaviour; the disease itself may also induce unadjusted behaviour, such as reduced water intake or inappropriate clothes in subjects with Alzheimer's disease or psychosis. However, knowledge about the exact underlying mechanisms is not necessarily required since in a clinical and pragmatic perspective, subjects using these drugs have to be considered at higher risk of heat-related diseases and carefully monitored during heat wave periods. Some cases may have been missed, since relevant clinical information was not always reported in medical charts in this crisis context. Indeed, it was not possible to assess the impact of dosage or dose on the risk of heat-related since such information was not available in most records. However, the purpose of the study was not to assess the prevalence of heat-related diseases. Controls were considered exposed if they had at least one refunding of prescribed drugs during the month preceding the heat wave. This selection had two consequences. First it was not possible to ascertain that the patients had actually taken the refunded drugs. Second, all controls were using at least one drug, while this criterion was not required for the cases. Hence, compared to subjects from the general population, controls were more likely to use drugs in general, and psychotropic drugs in particular. These two factors may have contributed to decrease rather than increase the strength of the associations. Lastly, we were not able to control for a range of possible and plausible confounders, as subjects treated for psychiatric diseases are also more likely to present with comorbidities, social isolation, poverty and the absence of air-conditioning.

6. Conclusion

Our results highlight the negative impact of psychotropic drugs which could interfere with body temperature regulation during heat waves and the need to assess the risk/benefit ratio of such treatment, particularly in the elderly.

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