The chlorpropamide alcohol flush

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Introduction

Many non-insulin dependent diabetics (NIDDs) on the sulphonylurea chlorpropamide experience intense facial flushing after taking alcohol even in small amounts. This chlorpropamide alcohol flush (CPAF) was first recognized within months of the introduction of the drug in the 1950s [1] but, although an alcohol flush occasionally occurs with tolbutamide [2, 3], it has not been reported with other sulphonylurea drugs.

CPAF is a flush of the face and neck, sometimes involving the conjunctivae. A few patients also describe a warmth and fullness of the hands but the flush is not seen elsewhere. Wheezing may also occur in those with pre-existing asthma [4, 5]. The reaction is not distressing although it is often embarrassing.

CPAF starts within 10-15 min of taking alcohol, reaches a peak in about 30 min and lasts for more than 90 min. It may be associated with a small increase in pulse rate but there is no change in blood pressure or sweating. CPAF begins within 2-5 days of starting chlorpropamide, continues for as long as it is taken and ceases within 4-7 days of stopping the drug. It does not appear to be dependent on the dose of alcohol, the rise of facial temperature being the same for doses of sherry varying from 10 to 100 ml, unlike simple alcohol flush which is dose dependent [6] (although in one recent study when a second, larger dose of alcohol was given the response increased [7]).

When CPAF was first recognized it was regarded as a harmless side effect until 1978 when it was observed in a mother and her two daughters with 'Mason-type' diabetes [8], a form of diabetes with dominant inheritance and relative freedom from complications [9]. Further reports [8, 10] suggested that CPAF was (1) dominantly inherited, (2) associated with familial non-insulin dependent diabetes, (3) more common in non-insulin dependent diabetics than in insulin dependent diabetics (IDDs) or non-diabetics and (4) was associated with a relative freedom from diabetic complications.

Assessment of chlorpropamide alcohol flush

Subject/observer

Subjective assessment of flushing by the patient was the only criterion used in the early studies. Although the patient is often aware of facial flushing this is not always the case; assessment by subject and observer together is more reliable. In a study of CPAF in NIDDs we have found that subject and observer agreed on the presence or absence of a flush in 109 of 120 tests (91%) (P. G. Wiles & D. A. Pyke, unpublished work).

Facial temperature

The facial flush results from an increase in skin blood flow and is reflected in a rise in facial temperature [11]. However, the rise is inversely related to the basal temperature so a definition of CPAF using an arbitrary temperature rise may not be satisfactory: an increase in blood flow will have less effect on skin temperature if the starting temperature is high, although patient and observer may still detect a facial flush (Fig. 1).

The temperature rise may be expressed as a percentage of the possible temperature increase,
Basal temperature (°C)

FIG. 1. Basal temperature vs temperature rise in 120 non-insulin dependent diabetics after chlorpropamide and alcohol in flushers (○, \( n = 61, r = -0.68, y = 17.6 - 0.5x \)), intermediates (in whom subject and observer disagreed on the presence of a flush) (○, \( n = 11, r = -0.28, y = 3.2 - 0.1x \)), regression line not shown), and non-flushers (○, \( n = 48, r = -0.45, y = 3.8 - 0.1x \)).

assuming a maximum skin temperature of 36.5°C, i.e.

\[
\text{% rise} = \frac{T_{\text{max}} - T_{\text{basal}}}{36.5 - T_{\text{basal}}} \times 100
\]

Those who flush, as agreed by subject and observer, have a value of at least 35%.

Other methods of expressing rise in facial temperature have been considered, change in malar thermal circulation index [12], or rate of rise of skin temperature [13, 14], which may be more accurate measures of change in skin blood flow than is temperature rise.

Persons who are CPAF positive as assessed by subject and observer ("flushers") and those who are CPAF negative ("non-flushers") have similar basal temperatures. Flushers show significantly greater rises in facial temperature after chlorpropamide and alcohol than non-flushers whatever the starting temperature (Fig. 1). However, at higher starting temperatures when temperature rises are small it is less easy to distinguish between flushers and non-flushers and CPAF is therefore best tested for when the resting facial temperature is less than 32°C.

**Thermography**

Thermography provides a good distinction between flushers and non-flushers. In ten patients in whom change in skin temperature was measured simultaneously by thermography and thermocouple there was no overlap between flushers and non-flushers as measured by thermography whereas there was as assessed by thermocouple [15]. However, the apparatus is expensive and not widely available.

**Plasma acetaldehyde**

Flushers show a greater rise of plasma acetaldehyde than non-flushers [16] (see below).

**Chlorpropamide dose**

The plasma level of chlorpropamide rises with increasing dose and duration of chlorpropamide treatment (Table 1) although there are wide variations among individuals [17-19]. Plasma levels 12 h after a single tablet of chlorpropamide (250 mg) are 22.6 ± 0.9 mg/l (mean ± SEM); after 7 and 14 days the values are similar (73.6 ± 6.4 mg/l and 68.3 ± 3.2 mg/l respectively) (Table 1) and resemble those after 250 mg twice daily for 2 days [13], which is therefore probably an adequate challenge.

There is no difference in chlorpropamide handling between flushers and non-flushers: in both plasma chlorpropamide levels are similar after 1, 7 and 14 days medication (Table 1) [20, 21], as are chlorpropamide kinetics [15], nor are there differences in plasma levels of the chlorpropamide metabolite chlorobenzylsulphonylurea [13].

There is a weak overall correlation between plasma chlorpropamide levels and rise in facial temperature [7, 17, 19] but above 40 mg/l we have found no further correlation. Thus, a chlorpropamide dose that achieves a plasma level of 40 mg/l or above should detect all potential flushers (P. G. Wiles & D. A. Pyke, unpublished work). Increasing the plasma chlorpropamide level still further does not convert non-flushers into flushers [22].

**Testing for chlorpropamide alcohol flush**

CPAF is best tested for using a dose of chlorpropamide which produces a plasma level of greater than 40 mg/l, i.e. 250 mg twice daily for 2 days or 250 mg daily for 7 days. Only a small dose of ethanol is needed: we use 8 g in 100 ml of fruit juice. Room temperature should be no more than 21°C, low enough to induce a facial temperature of 32°C or below. For clinical studies no single criterion is enough to diagnose CPAF, therefore we and others [13, 23] have used the arbitrary criteria of (1) the subject’s awareness of facial warmth, (2) the appearance of an observable flush and (3) a temperature rise of 1°C or more. We now favour using the criterion of 1.5°C with a
starting temperature below 32°C or 35% of the possible temperature rise.

### Frequency

Widely varying frequencies of chlorpropamide alcohol flushing have been reported. Earlier reports, based on clinical assessment, put the frequency at 15–30% for diabetics on chlorpropamide treatment \([1, 24]\). More recent estimations have varied between 4 and 65% \([14, 23]\). This variation has been attributed to simple alcohol flushing \([13]\), basal temperature differences \([25]\) and differences in plasma chlorpropamide levels \([17,26]\).

The issue remains in doubt. In our own recent studies we found in 40 NIDDs a frequency of 30% 12 h after a single tablet of chlorpropamide (250 mg) and 73% after 250 mg of chlorpropamide daily for 14 days \([20]\). In IDDs using a 7 day test (which produces plasma chlorpropamide levels similar to the 14 day dose) we found a CPAF frequency of 40% in 50 patients (P. G. Wiles & D. A. Pyke, unpublished work). Previous studies in IDDs, using single tablet tests only, have found frequencies of 5–16% \([8, 13, 27]\) and studies in NIDDs, with most subjects taking chlorpropamide long-term, showed frequencies of about 65% \([24, 28]\). Thus (1) in both IDDs and NIDDs prolonged pretreatment with chlorpropamide increases the frequency of CPAF, and (2) with similar chlorpropamide levels NIDDs seem to show a higher frequency of CPAF than IDDs. However, a recent epidemiological study found approximately similar frequencies of CPAF in NIDDs, IDDs and non-diabetics \([29]\). This study used a single tablet test which, it is now clear, is not adequate in all cases and depended on subject self-assessment which may not allow for differences in intensity of flushing. Nevertheless the study did show a twofold increase in overall frequency of flushing after chlorpropamide and alcohol in NIDDs compared with IDDs and non-diabetics \([30]\). Objective measurements under control conditions to settle the question of the relative frequencies of CPAF in NIDDs, IDDs and non-diabetics are still needed.

The frequency of CPAF in non-diabetics has been investigated only with single challenge tests when rates of less than 10% were obtained \([8, 28]\). The rate may be greater if a higher plasma level of chlorpropamide is achieved although this might carry the risk of hypoglycaemia and has not yet been done.

An increased frequency of CPAF among women has been reported \([13, 23, 31]\).
Mechanisms

Acetaldehyde

Ethanol is oxidized to acetaldehyde by alcohol dehydrogenase (ADH) and then to acetate by aldehyde dehydrogenase (ALDH). ALDH is inhibited by disulfiram and chlorpropamide (and to a lesser extent by tolbutamide) [32].

The similarity between CPAF and the antabuse (disulfiram) reaction led to measurements of plasma acetaldehyde during CPAF. Early results were variable [24, 33] but with improved assay techniques it has now been demonstrated that there is a rise in plasma acetaldehyde following chlorpropamide and alcohol which is greater in flushers than non-flushers [21, 34].

Disulfiram and alcohol produce a greater rise in acetaldehyde in flushers than non-flushers [35]. Acetaldehyde is metabolized more slowly in vitro by erythrocyte homogenates from flushers than from non-flushers [36] and erythrocyte ALDH activity is reduced in vivo by chlorpropamide in flushers but not in non-flushers (P. G. Wiles & D. A. Pyke, unpublished work). There is, however, no structural difference in ALDH, as shown by electrophoretic studies of liver biopsy specimens, in flushers and non-flushers [15].

Opioids

The chlorpropamide alcohol flush may be reproduced by the metenkephalin analogue DAMME (D-Ala² methy1⁴ Met(O)-ol enkephalin) and blocked by naloxone [37]. Circulating metenkephalin has been shown to rise following chlorpropamide and alcohol [38]. A similar rise occurs in diabetics and non-diabetics, flushers and non-flushers; thus CPAF might be mediated by a sensitivity to a rise in circulating met-enkephalin. However, we have found that intravenous naloxone does not block the rise in met-enkephalin even in those patients in whom it does block the flush. In addition, intravenous ethanol can induce a chlorpropamide alcohol flush but it does not lead to a rise in plasma met-enkephalin (P. G. Wiles and others, unpublished work). Thus a rise in circulating met-enkephalin is unlikely to mediate CPAF.

The activity of endogenous opioids may be altered by acetaldehyde [39], which suggests a link between the rise in acetaldehyde during CPAF and the possible involvement of opioids in the mediation of CPAF.

Other possible mediators of CPAF which have been investigated and found to show no change during CPAF include blood kinins [40], serotonin and dopamine [13].

Prostaglandins

CPAF may be blocked by prostaglandin synthetase inhibitors such as aspirin [41], naproxen [42] and indomethacin [43], suggesting that prostaglandins may mediate CPAF. A rise in both prostacyclin [44] and thromboxane [45] has been reported after chlorpropamide and alcohol, greater in flushers than non-flushers, but there are no differences in basal levels of circulating prostanooids. Methods for measuring circulating prostanooids are difficult and these results should be interpreted with caution.

Metabolic studies

Little difference can be demonstrated between flushers and non-flushers in (1) serum insulin and blood metabolite response to oral glucose, (2) blood lipids or (3) haemostatic mechanisms [31, 46]. Flushers and non-flushers may show a difference in insulin secretion in response to an infusion of naloxone; in flushers it may be suppressed by a low dose bolus injection and infusion [47] although not by higher doses [46, 48]. There is no difference between flushers and non-flushers in their β-cell response to salicylate infusion [48].

Inheritance

Early studies suggested a greater frequency of CPAF in NIDDs with a strong family history of diabetes [10, 23] although other reports have not confirmed this [11, 31]. Studies in Mason-type families suggested an autosomal dominant mode of transmission of CPAF [8] but not in other families with maturity onset diabetes of youth (MODY) [49, 50]. Thus CPAF may be a dominantly inherited feature only in some subtypes of MODY. Identical twin pairs show concordance for CPAF itself and for blocking by indomethacin irrespective of concordance for diabetes [8, 43].

The insulin gene and neighbouring areas on the short arm of chromosome 6 show variations in the 5′ flanking region of the insulin gene with the presence of long (U) and short (L) inserts. NIDD has been reported to be associated with the U allele [51] but we have found no association between CPAF and the U or L allele. However, we cannot certainly exclude the possibility of an association between CPAF and the UL heterozygote [52].

Diabetic complications

When we found that CPAF was associated with Mason-type diabetes, in which complications are
uncommon [8, 9], we investigated the association between CPAF and diabetic complications. Flushers have been reported to show relative freedom from retinopathy [27, 28], proteinuria [53], macroangiopathy [23, 27, 31, 54] and neuropathy [23]. Flushers whose reaction can be blocked by indomethacin seem to be particularly protected from vascular complications [43]. These studies, however, were performed at a wide range of chlorpropamide levels. Other studies have shown no difference between flushers and non-flushers in the frequency of retinopathy [31] or macrovascular disease [55]. Until studies of large numbers of patients using both single challenge and higher dose chlorpropamide tests have been performed we cannot confidently decide whether flushers are less likely to develop complications than non-flushers.

The majority of the Mason-type diabetics seem to be positive on the single tablet CPAF test [10]. They are usually free of complications. Thus the single challenge test may prove to be the best in distinguishing those flushers who have relative protection from complications.

Conclusions

What, then, is the evidence for the chlorpropamide alcohol flush having clinical, genetic or metabolic significance?

CPAF is common among NIDDs; it is also found in IDDs and non-diabetics, its relative frequency still being a matter of doubt. The single chlorpropamide tablet test may identify a subgroup of diabetic patients who are relatively protected from complications. CPAF testing is not yet sufficiently specific to be used in identifying potential diabetics.

CPAF may be dominantly inherited, at least in certain families. In them it might prove useful in identifying family members at risk from diabetes.

There is a difference in acetaldehyde level after chlorpropamide and alcohol between flushers and non-flushers. The blocking of CPAF by prostaglandin synthetase inhibitors and naloxone implicates prostaglandins and endogenous opioids in the mediation of CPAF. There is also a suggestion that among NIDDs the β-cell response to endogenous opioids may be different in flushers and non-flushers.

Whatever the deficiencies in our knowledge and understanding of CPAF there can be little doubt that it is a real phenomenon with potentially important biochemical and endocrine implications.

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References


