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Controversial topics

Chlorpropamide – alcohol flush: the case in favour

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In this review, written at the Editor's invitation, we shall describe the chlorpropamide alcohol flush, how it is assessed, its possible mechanism and inheritance, and its significance in relation to diabetic complications and the pathogenesis of Type 2 (non-insulin-dependent) diabetes itself. There are many matters of doubt, even of controversy, which we shall discuss. There are also many points of certainty, or so we believe, and we shall start with them.

The chlorpropamide – alcohol flush (CPAF) exists. It consists of a flush of the face sometimes spreading to the neck which may be accompanied by injection of the conjunctivae. The flush is visible to observers as well as being felt by the subject. It may be so intense that it gives a burning sensation and, very rarely, a headache. CPAF is not accompanied by sweating or prostration although in a few patients it is associated with wheezing, but it is often embarrassing. The reaction starts within 10 or 20 min of taking alcohol, reaches its peak at 30–40 min and persists for 1–2 h or more. CPAF is different from the flush due to alcohol alone; patients who have experienced both are in no doubt of their difference.

Although as with all clinical phenomena there is individual variation, the reaction is generally consistent, coming on every time alcohol is taken. The amount of alcohol needed to provoke the flush is small – no more than half a glass of sherry or wine. Larger quantities of alcohol do not provoke a more intense flush, in distinction from simple alcohol flushing whose intensity varies directly with the amount of alcohol consumed [1].

CPAF appears soon after the start of chlorpropamide treatment and persists for as long as it is continued; when chlorpropamide is stopped the reaction invariably ceases within a few days. Alcohol flushing has occasionally been described with tolbutamide, but hardly ever with other sulphonylureas.

CPAF was first reported within a few months of the introduction of chlorpropamide treatment in the 1950's. At a meeting of the New York Academy of Sciences on chlorpropamide in 1959 there were 47 clinical papers from many different countries [2]. Eight contained clear descriptions of CPAF, while one was entirely concerned with it and included measurements of blood flow in the ear which was shown to be greater in susceptible subjects after chlorpropamide and alcohol than after alcohol alone [3]. In those early papers, various figures for the frequency of CPAF were given, most being of the order of 15%–30%. A systematic study of 100 Type 2 diabetic patients taking chlorpropamide gave a figure of 33% [4]. These results derive from Caucasoid populations and are based on direct questioning of diabetic subjects taking regular chlorpropamide.

Some authors have suggested that CPAF is less common than this [5, 6]. They believe that most cases of so-called CPAF are really simple alcohol flushing, or that previous figures have been exaggerated by direct questioning of patients when the answer may unwittingly have been suggested by the questioner.

Uncertainty exists on how CPAF is best tested for, its mechanism, whether it is inherited, whether it is associated with certain types of diabetes – even with diabetes at all – and whether it is associated with a relative freedom from diabetic vascular complications.

Testing for chlorpropamide alcohol flushing

Our interest in CPAF was aroused when we discovered that a mother and daughter with 'Mason-type' diabetes, a variety of 'MODY' (maturity-onset diabetes of youth), both reported definite CPAF [7]. When we tested other members of this and similar families there was a very strong association between diabetes and CPAF, 33 of 38 diabetic relatives reporting CPAF whereas only two of 36 non-diabetic relatives did so. The assessment of CPAF in these cases was based on their reports of the response to a glass of sherry taken 12 h after one tablet of chlorpropamide (250 mg) except in those patients who were already on regular chlorpropamide treatment.

It soon became clear that CPAF was not confined to 'Mason-type' diabetes [8]. However, because CPAF was such a feature in the Mason-type families, and because as many of these patients seemed to be positive when given only one tablet of chlorpropamide as when on regular daily treatment, we assumed that the reaction could be satisfactorily elicited by a single chlorpropamide tablet. We now know that this was an error and that the dose of chlorpropamide influences the frequency of a positive response.

To assess the effect of the dose of chlorpropamide we tested 30 Type 2 diabetic patients 12 h after a single tablet of 250 mg, and again after 2 weeks' treatment with 250 mg daily. Flushing was assessed by subject and observer. After one tablet, seven (23%) flushed with 8 g ethanol; after 2 weeks 22 (73%) did so. These patients were selected and may have included a disproportionate number of CPAF-positive subjects, hereafter referred to as 'flushers'.

A satisfactory test for CPAF should probably include 8 or 9 days' pretreatment with chlorpropamide (250 mg daily), the time required to reach a steady blood level, five times the half life. However this raises problems in testing normal subjects in whom such a dose might lead to hypoglycaemia.

How should CPAF be assessed? The reaction comprises an increase of skin blood flow leading to a rise of facial temperature and a flush. It could therefore be measured by the patient's own feelings (ascertained by direct questioning or questionnaire), by observation or by assessment of facial blood flow. This could be measured either directly at a single point by a thermocouple, or measured as the mean integrated temperature response of a larger area (e.g. forehead) by using thermography.

The subject's own awareness of a flush is often definite and it is then usually associated with visible reddening of the face. We have compared patients' subjective awareness of a flush with the opinion of an observer (Table 1). In 30 Type 2 diabetic patients tested after a single tablet of chlorpropamide and 8 g of ethanol, there was agreement between subject and observer in 27, of whom seven flushed and 20 did not; when tested after 2 weeks' chlorpropamide treatment, there was agreement in 26, of whom 22 flushed and four did not. In the three and four cases respectively in which there was disagreement, it was in both directions. It was as often the observer who thought there was a flush when the subject did not as vice versa.

The joint assessment of observer and subject also correlated fairly well with rise of cheek temperature. In the single-tablet series only six of 20 non-flushers showed a temperature rise of over 1 °C and none over 1.4 °C; on the other hand, five of the seven flushers showed a rise of over 1.0 °C (three over 1.4 °C). In three cases in which there was disagreement between observer and subject, the rises were 0.6 °C, 0.9 °C and 1.5 °C. After 2 weeks' chlorpropamide all four of the non-flushers showed a temperature rise of less than 1 °C; of the 22 flushers, 21 showed a rise of over 1 °C, 17 of over 1.4 °C. Thus in this group, 21 flushers but no non-flushers showed a rise of over 1 °C, while one flusher and the four non-flushers showed a rise of less than this figure.

Table 1. Increase in facial temperature in 30 patients tested for chlorpropamide alcohol flushing by 8 g of ethanol after one tablet of chlorpropamide or 14 days' treatment

	After chlorpropamide (250 mg)			After 14 days' chlorpropamide (250 mg daily)		
	Temperature rise (°C)			Temperature rise (°C)		
	0–0.9	1–1.4	1.5–3.5	0–0.9	1–1.4	1.5–5.0
Flushers	2	2	3	1	4	17
Doubtful[a]	2	0	1	0	3	1
Non-flushers	14	6	0	4	0	0

[a] Patient and observer disagreed

Table 2. Changes in facial temperature measured by thermocouple and thermography in 10 subjects (five previously assessed as flushers, five as non-flushers) after 2 weeks' chlorpropamide (250 mg daily) and a single dose of ethanol (8 g)

	Basal	Maximum	Rise	p
Thermocouple (°C)				
Flushers	32.4 ± 0.5	35.3 ± 0.2	2.9 ± 0.5	< 0.01
Non-flushers	32.5 ± 0.7	33.4 ± 0.6	0.9 ± 0.3	
Thermography (units)				
Flushers	46.8 ± 1.1	56.2 ± 1.4	9.4 ± 1.4	< 0.01
Non-flushers	43.2 ± 2.8	45.4 ± 2.8	2.2 ± 0.7	

Results expressed as mean ± SEM

Measurement of the rise in temperature is not entirely satisfactory as it is (inversely) related to basal temperature [9]. An increase of skin blood flow will have more effect on temperature if the starting temperature is low than if it is high. Could the difference between flushers and non-flushers lie not in their response to the alcohol challenge but in their resting facial temperature, flushers starting cooler and therefore showing a greater response to alcohol? To test this suggestion, we studied ten diabetic patients, five previously classified as flushers, five as non-flushers. With similar starting temperatures the flushers showed a rise after ethanol three times greater than the non-flushers (2.9° versus 0.9 °C; Table 2).

Measurement of facial blood flow by thermography in the same ten patients gave an even sharper division between flushers and non-flushers. The five flushers, who started at a slightly higher basal reading, showed a response to alcohol four times that in the non-flushers and there was no overlap between the two groups (Table 2).

Thus it seems that (1) 2 weeks' pretreatment with chlorpropamide (250 mg daily) gives a greater frequency and more intense alcohol flush than a single tablet; (2) assessments of the flush by patient and observer

Table 3. Chlorpropamide kinetics in flushers and non-flushers

	After chlorpropamide (250 mg)		After 14 days' chlorpropamide (250 mg daily) Concentration (mg/l)
	Peak concentration (mg/l)	Elimination half life (h)	
Flushers ($n=11$)	21.6 ± 1.4	39.4 ± 3.9	91.7 ± 10.7
Non-flushers ($n=9$)	23.9 ± 2.0	37.5 ± 5.1	78.3 ± 12.6

Results expressed as mean ± SEM

agree in about 85% of cases; (3) there is a significantly greater rise of facial skin temperature in flushers than in non-flushers; (4) this difference is not due merely to difference in basal temperatures; and (5) thermography may be a better index of facial skin blood flow than thermometry.

The inheritance of CPAF

The close association of CPAF with 'Mason-type' diabetes, which seems to be inherited as an autosomal dominant trait, suggested that CPAF too might be dominantly inherited and evidence from twin and family studies seems to confirm this [7, 8]. However, most of these studies were carried out on strongly positive flushers who reacted to a single tablet challenge test. It is possible that less responsive flushers, i.e. those who react only when given several days' chlorpropamide, might show a different pattern.

Mechanism of CPAF

Blood levels of chlorpropamide

The blood level of chlorpropamide may be relevant to CPAF in that longer treatment, and therefore higher blood levels, are needed in some individuals than in others to produce the reaction. Flushers and non-flushers given the same dose of chlorpropamide show different temperature responses (Table 2). This could not be due to different chlorpropamide levels unless the two groups metabolised chlorpropamide differently. The original suggestion that they do [10] was based on a comparison of serum chlorpropamide levels in patients of whom some had taken only one tablet while others were on maintenance treatment.

We have studied plasma chlorpropamide levels after a single tablet of 250 mg and after 14 days' treatment in 11 diabetic patients who had been classed as flushers and nine as non-flushers. (Table 3). The values are similar in flushers and non-flushers and we do not believe, therefore, that differences in chlorpropamide handling explain CPAF.

Autonomic neuropathy and CPAF

It has been suggested that autonomic neuropathy plays a part in the production of CPAF or protection from it [9]. However, we doubt this because we have excluded from our studies diabetic patients known to have this complication, and because CPAF is seen in non-diabetic subjects.

CPAF and acetaldehyde levels

As CPAF resembles the flushing produced by disulfiram, soon after the phenomenon was recognised the possibility was raised that it too might be produced by increased levels of acetaldehyde in the blood [4]. Alcohol is metabolised to acetaldehyde under the influence of alcohol dehydrogenase and then to acetate under the influence of aldehyde dehydrogenase (ALDH), an enzyme which is inhibited by disulfiram. Chlorpropamide (and to a lesser extent tolbutamide) also inhibits ALDH [11]. Early studies showed no increase of acetaldehyde concentrations during CPAF [4], but with improved techniques it has been shown that blood levels of acetaldehyde after chlorpropamide and alcohol are indeed higher in flushers than in non-flushers [12, 13]. Blood acetaldehyde may be the most reliable tool for investigating CPAF, but its measurement is still difficult and time consuming.

The elevation of blood acetaldehyde concentrations suggested that CPAF might be due to a variation of ALDH. Simple alcohol flushing is common in the Japanese and Chinese who frequently show an 'atypical' variant of ALDH which is probably the explanation for the alcohol flushing [14].

Could the CPAF be due to a similar variation? We do not think so because (1) the oriental type of ALDH has never been found in occidentals [15]; (2) we have examined ALDH in liver biopsy specimens and have not found the atypical enzyme in those cases which showed CPAF. However, flushers seem to be more sensitive to the effect of disulfiram than non-flushers. When given alcohol after 4 days, disulfiram (200 mg daily) both groups showed a flush, but in six chlorpropamide alcohol flushers the increase of plasma acetaldehyde was twice that in nine non-flushers (0.92 ± 0.15 versus 0.47 ± 0.06 mg/l, mean ± SEM, $p < 0.01$). Furthermore there is evidence that ALDH may be functionally different in flushers: if acetaldehyde is added to a homogenate of red cells, its rate of disappearance is slower in samples taken from flushers than non-flushers [16]. ALDH in flushers may therefore be more sensitive to the inhibitory effect of chlorpropamide.

Opioids and CPAF

That CPAF might be related to the effect of opioids was suggested by the finding that flushers show a greater rise of facial temperature when given a met-enkephalin

analogue intravenously than do non-flushers and that, in some cases at least, CPAF can be blocked by the opiate antagonist naloxone [17]. We speculated that CPAF might be due to an increased sensitivity to circulating enkephalin (or other opioid peptides).

This seemed to be partially confirmed by the finding that chlorpropamide and alcohol lead to a rise in plasma met-enkephalin levels which occurs in diabetic and non-diabetic subjects, flushers and non-flushers [18]. However, if alcohol is given intravenously there is no longer any rise of met-enkephalin, but there is still a flush. Furthermore, naloxone, while blocking the flush, does not prevent the rise of blood met-enkephalin (unpublished observations). Thus CPAF cannot be due to sensitivity to met-enkephalin.

Nevertheless, chlorpropamide with alcohol remains the only stimulus which raises plasma met-enkephalin levels, and a possible relationship between CPAF and opioid peptides is worth pursuing.

Tetrahydroisoquinolines

The demonstration that both acetaldehyde and met-enkephalin rise during CPAF and that these rises persist despite blockade of the reaction by naloxone made it difficult to postulate a uniform theory for the mechanism of the reaction. A possible link between an opiate effect and acetaldehyde is the formation of tetrahydroisoquinolines. These compounds are formed from Pictet-Spengler condensation reactions between acetaldehyde and endogenous amines [20] and they have a wide range of pharmacological effects, including opiate-like activity [21]. We have preliminary data suggesting that the formation of tetrahydroisoquinolines is increased in CPAF and that this increase is abolished when the flush is blocked.

CPAF and the incidence of diabetic vascular complications

We originally became interested in CPAF because it is common in 'Mason-type' diabetes. One of the features of these cases is their low frequency of diabetic complications. We wondered therefore whether CPAF in Type 2 diabetes generally was associated with a low incidence of complications.

We found that it was [22–24]. Flushers showed less microvascular and macrovascular disease than non-flushers. The 'protection' associated with CPAF is only partial. We have seen several flushers with well-marked retinopathy and other complications.

The relative freedom from complications has been confirmed by some [25] but not by others [26]. The apparent discrepancy may be due to different doses of chlorpropamide being used to elicit the reaction. The connection between CPAF and vascular complications remains to be fully elucidated.

Prostaglandins

Inhibitors of prostaglandin synthesis, such as indomethacin [27], aspirin [28] and naproxen [12], have also been shown to block the flush reaction, especially in those patients free of complications [27]. This raises the possibility that prostaglandins might be involved in the mediation of CPAF and the complications of diabetes. A rise in prostacyclin [29] and/or thromboxane [30] has been reported in those positive for CPAF, but in view of the present uncertainty of the methods employed these results should be interpreted with caution.

Conclusions and speculations

The investigation of CPAF started from a simple phenomenon, a harmless side effect of a drug. It may have nothing to tell us about the management of diabetes, but we suspect that understanding its mechanism may throw light on genetically determined differences between Type 2 diabetic patients and normal subjects and that these in turn could be relevant to the production of the vascular complications of the disease. The possible connection of CPAF with opioid peptides has reminded us of the relationship between the brain and blood glucose control, first reported by Claude Bernard 130 years ago, of which there has been much recent supporting evidence [31–34]. This relationship could have a bearing on the pathogenesis of Type 2 diabetes.

We believe that the trail is worth following.

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