Diabetologia (1984) 26: 12–14

Diabetologia

Controversial topics

To flush or not to flush? Comments on the chlorpropamide-alcohol flush

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Flushing, nausea and some giddiness were observed in diabetic patients following their exposure to chlorpropamide and alcohol as early as 1959, shortly after chlorpropamide's release for clinical use [1]. Some 20 years later this phenomenon, which undoubtedly does exist, has been restudied in detail and described as occurring more often in Type 2 (non-insulin-dependent) diabetes than in Type 1 (insulin-dependent) diabetes or in healthy man [2, 3]. In particular, chlorpropamide-alcohol-flushing (CPAF) was seen to a greater extent (81%) in patients with a family history of Type 2 diabetes [3]. Against this background CPAF was consequently used as a tool to define better the heterogeneity of Type 2 diabetes as well as the prognosis of the associated late complications [2, 4, 5]. These studies finally led to a controversy, which is reflected by the contributions to this issue of Diabetologia [6–8]. The major points of disagreement in the course of the debate focus on the usefulness of CPAF as a defined test procedure for studying the heterogeneity of Type 2 diabetes.

Trying to comment on the present state of the art of chlorpropamide-alcohol-flushing one rapidly becomes aware that 'flushing' is a relatively common phenomenon. It occurs for a variety of causes, which include chemical agents as well as a broad range of clinical conditions (Table 1), all of which finally lead to stimulation of vascular smooth muscle or vasomotor nerves. Thus "hot flushes" are the most frequent complaint associated with the menopause and occur in about 80% of women [9], but are also present in some rare clinical syndromes including rosacea and carcinoid tumours [10]. Among the compounds provoking flushing, alcohol [10], nicotinic acid [11], catecholamines [12, 13] and others [10] are well known. In addition, genetic and environmental factors affecting ethanol metabolism [14] may contribute to the occurrence of alcohol flushing. Therefore, accumulation of acetaldehyde, as seen following alcohol ingestion as well as during CPAF [15] and even more so after administration of disulfiram [16], has been thought to be responsible for flushing. This assumption is, however, subject to doubt as no relation was found between circulating acetaldehyde levels and the severity of flushing in ethnic groups which are genetically predisposed to flushing [17].

The underlying biochemical and/or neurological changes responsible for the induced vasodilatation are still unknown, although many compounds have been discussed as possible mediators of 'flushing' (Table 2).

Table 1. Compounds and clinical conditions associated with flushing

Compounds		Syndromes	
β-adrenoceptor agonists	[21]	Carcinoid syndrome	[21]
Alcohol	[10]	Eating	[21]
Calcium carbamide	[18]	Excitement	[21]
Carbon monoxide	[20]	Mastocytosis	[10, 22]
Chlorpropamide	[1, 2]	Medullary carcinoma of the thyroid	[22]
Disulfiram	[10]	Menopause	[9]
Glucose	[19]	Non-insulin-dependent diabetes	[2]
Glutamate	[10]	Rosacea	[23]
Griseofulvin	[18]	Vipoma	[22]
β-lactam antibiotics	[10]		
Metronidazole	[18]		
Nicotinic acid	[11]		
Pentagastrin	[20]		

Table 2. Postulated mediators of flushing

Compound	Remarks
Acetaldehyde	Elevated during CPAF [15, 29]
Histamine	H_1 and H_2 receptor blockers are required to suppress a flush. Most likely a pharmacological action only [12, 28]
Kallikrein	Parallels flushing in patients with carcinoid tumour [27]
Lysyl-bradykinin	Mimics spontaneous flushes and is elevated during adrenaline-induced flushes [13, 25]
Met-enkephalin	Elevated during CPAF [30]
Prostaglandins	Thromboxane and prostacyclin are elevated during CPAF [26]
Serotonin	May or may not be elevated during flushing [12]
Substance P	Occurs naturally in enterochromaffin cells [10]

Table 3. Reported prevalence of chlorpropamide-alcohol-flushing in Type 2 diabetic patients and healthy control subjects

Reference	Type 2 diabetic patients		Control subjects		Chlorpropamide (mg)	Sherry (ml)
	Prevalence		Prevalence			
	(%)	(*n*)	(%)	(*n*)		
Micossi et al. [32]	33[a]	108		0	250	40
Köbberling et al. [33]	15.3	131	16.9	154	2 × 250	20
	17.7[d]	62				
Leslie and Pyke [3]	81[d]	91	10	60	250	40
	31[e]	143				
Jerntorp et al. [34]	65	70		0	125–375	8 g alcohol
de Silva et al. [35]	22[b]	49	38[c]	21	250	40

After correction for placebo instead of chlorpropamide: [a]17%; [b]4%; [c]10%.
[d]with, [e]without first degree family history of Type 2 diabetes
n = total number of subjects studied

One of the first agents thought to be responsible was serotonin, which is elevated in patients carrying a carcinoid tumour, but may or may not be elevated in plasma during flushing [12]. Furthermore, it has been suggested that flushing may be provoked by minute amounts of catecholamines [12], which possibly induce the release of vasodilating agents such as kallikrein [24] and lysyl-bradykinin [13]. This is of note as lysyl-bradykinin is able to mimic spontaneous flushes [25]. A role in flushing has also been suggested for a rise in histamine [12] as well as prostaglandin release [26]. As CPAF may be abolished by the opiate antagonist naloxone and flushing is mimicked by an analogue of the opioid peptide met-enkephalins it has been suggested that flushing results from an increased sensitivity to endogenous opiates [31]. From this overall pattern we have to conclude that many compounds may be able to provoke flushing and that the final cause of CPAF remains to be explored.

Against this background it also becomes obvious that the transient phenomenon of facial flushing, as it occurs in some non-insulin-dependent diabetic patients after drinking alcohol when ingesting chlorpropamide, requires strict definition and quantification. The difficulty in fulfilling these requirements becomes apparent if flushing is defined according to Webster's dictionary as 'a tinge of red or ruddy colour as produced on cheeks', or as the patient's subjective perception of a 'warm, tingling or even burning sensation in the face' [3]. This difficulty in describing the flush is also reflected by the statement of Groop et al. [8] that they were 'unable to show significant differences between (previously) CPAF-positive and CPAF-negative patients regarding flush-score, rise in facial skin temperature and blood acetaldehyde'. It is this basic problem in standardizing a bioassay which explains the large discrepancies in the estimated prevalence of chlorpropamide-alcohol flushing in Type 2 diabetes (Table 3). Use of thermography may help to improve this situation [6], although the response to be observed is heavily dependent on initial cheek temperature [33, 36]. Furthermore, dependence of CPAF on chlorpropamide dose contributes to problems in testing as well as the need for a 8–9 day exposure to chlorpropamide [6], which also increases the risk of hypoglycaemia and thus hampers the recruitment of the necessary numbers of healthy control subjects. The preponderant use of undefined amounts of sherry, with all its ingredients, instead of the compulsory use of a defined amount of alcohol, likewise does not help the standardization of the test. Attempts to improve these basic limitations of the CPAF concept have been further jeopardized by the observation that one can flush without a rise in skin temperature, while conversely, a rise in temperature may occur without visible flushing [37]. These difficulties in defining objective, i.e. measurable criteria for CPAF so far appear insurmountable and make any investigator completely dependent on the patient's interpretation of his subjective feelings. Thus at present the situation argues against employing CPAF as a means for the selection and definition of patients for epidemiological studies, as for example the evaluation of the frequency of late diabetic complications [5].

Surprisingly, less disagreement seems to exist as to the occurrence of CPAF in patients with Mason-type diabetes, i.e. mild familial diabetes with dominant inheritance [38]. Patients suffering from this syndrome displayed a relatively homogenous 57%–84% prevalence of CPAF [37], although again one contradictory study reported three out of four Mason-type diabetics to be CPAF-negative [39]. It may well be, however, that patients with Mason-type diabetes more often carry the fully developed trait for CPAF than do other non-insulin-dependent diabetic patients, and thus present a more homogenous group.

From the above one has to conclude that recruitment of CPAF-positive individuals is a tricky task if one starts with an otherwise undefined group of patients with Type 2 diabetes, as the definition of flushing is subject to considerable error unless new ways of standard-

ization are designed to overcome the obstacles of subjective monitoring of CPAF. Fortunately, the risk of selecting a heterogeneous group of CPAF-positive patients seems to be considerably smaller in Mason-type diabetics [37] than in patients with Type 2 diabetes. Thus it appears reasonable to study patients from this more homogenous group in a collective effort to design a reproducible test of chlorpropamide-alcohol flushing. Dosage of chlorpropamide and alcohol per kilogram body weight may help in standardization of the test. Only when a reproducible test for CPAF is available can the clinically exciting speculations that CPAF-positive diabetic patients carry a smaller risk than CPAF-negative individuals of developing the dreaded late complications of diabetes be proved or disproved.

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