one year of referrals and hence the numbers were small.[6] The second study covered three years and included larger numbers of babies, but only referrals made postnatally were considered. In both studies no account was taken of confounding variables that could influence neonatal mortality.

Our study of referrals to the regional perinatal centre included hospitals from all over Northern Ireland. Cross regional referrals are not made in Northern Ireland and it proved relatively easy to trace most (98·3%) of the obstetric and neonatal records during the three years. We also considered babies who were referred prenatally, and the only criterion for refusal was unavailability of an intensive care cot for neonates at the centre. As this was not a randomised study, we adjusted for confounding variables in comparing outcome in the groups.

Of babies initially refused admission to the centre, most (78·6%) were subsequently accepted into other neonatal intensive care units within Northern Ireland. There was no significant difference in outcome for babies managed in these units compared with those managed in the centre. In many cases, however, there was a considerable delay before babies refused admission to the centre could be given intensive care, and their long term outcome remains uncertain. We have shown previously that the incidence of handicap is significantly higher in babies referred for intensive care after birth compared with those accepted prenatally.[10] A delay in starting intensive care may therefore be important. Those babies who did not receive intensive care and remained in special care baby units had a greater than threefold increase in their odds on dying. In addition, survivors from these hospitals could be expected to have a higher incidence of handicap than those sent for intensive care, although follow up studies are needed to confirm this.

There was some imbalance in the indications for prenatal referral, particularly in the number of cases of pre-eclampsia and rhesus isoimmunisation. This reflects clinical practice in that delivery of mothers with these conditions can often be delayed until an intensive care cot becomes available.

The number of babies who needed intensive care but were refused admission may be an underestimate as obstetricians and paediatricians at the hospitals that refer such babies may have known that intensive care cots were not available at the centre and therefore did not request transfer. Examination of mortality related to birth weight in individual hospitals might clarify this further.

Our study confirmed the benefits of neonatal intensive care and its particular value in improving the survival of babies of low birth weight. Short term survival seemed to be similar in smaller neonatal intensive care units and the regional perinatal centre, but we did not look at long term outcome and handicap. Further studies are needed to determine the influence of delay in starting intensive care on short term outcome and handicap. Clearly, in Northern Ireland, as in other parts of the United Kingdom,[5] not enough neonatal intensive care cots are provided and the deficiency should be remedied as soon as possible.

1 Blake AM, Pollitzer MJ, Reynolds EOR. Referral of mothers and infants for intensive care. *Br Med J* 1979;ii:414-36.
2 Lobb MO, Morgan MEI, Bond AP, Cooke RWI. Transfer before delivery on Merseyside: an analysis of the first 140 patients. *Br J Obstet Gynaecol* 1983;**90**:338-41.
3 Powell TG, Pharoah POD. Regional neonatal intensive care: bias and benefit. *Br Med J* 1987;**295**:690-2.
4 Cooke RW. Where should low birthweight babies be born? *Br Med J* 1986;**293**:974-5.
5 Royal College of Physicians of London. *Medical care of the newborn in England and Wales*. London: RCP, 1988. (Report No 0-900596-79-1.)
6 Sims DG, Wynn J, Chiswick ML. Outcome for newborn babies declined admission to a regional neonatal intensive care unit. *Arch Dis Child* 1982;57:334-7.
7 Roper HP, Chiswick ML, Sims DG. Referrals to a regional neonatal intensive care unit. *Arch Dis Child* 1988;**63**:403-7.
8 Cox DR. *The analysis of binary data*. London: Methuen, 1970.
9 Patterson CC, Halliday HL. Prediction of outcome after delivery for the very low birthweight (≤1500 g) infant. *Paediatric and Perinatal Epidemiology* 1982;2:221-8.
10 Halliday HL, Patterson CC, McClure BG, Reid MMcC. Where should low weight babies be born? *Br Med J* 1986;**293**:1437.

(Accepted 6 July 1989)

Survey of colourings and preservatives in drugs

I Pollock, E Young, M Stoneham, N Slater, J D Wilkinson, J O Warner

Heart and Lung Institute, Brompton Hospital, London
I Pollock, MRCP, *research registrar*
J O Warner, FRCP, *consultant paediatric chest physician*

Department of Dermatology, Wycombe General Hospital, Buckinghamshire
E Young, MRCP, *senior registrar in dermatology*
M Stoneham MRCGP, *research assistant in dermatology*
N Slater, *computer technician*
J D Wilkinson, FRCP, *consultant dermatologist*

Correspondence to:
Dr I Pollock, Department of Child Health, St George's Hospital, London SW17 0RE.

Br Med J 1989;**299**:649-51

Abstract

***Objective*—To assess the prevalence of colourings and preservatives in drug formulations in the United Kingdom.**

***Design*—Postal survey.**

***Participants*—All pharmaceutical manufacturers in the United Kingdom were requested to supply data on drug formulations with particular regard to the content of colourings and preservatives.**

***Main outcome measure*—Prevalence in proprietary drugs of colourings or preservatives, or both, that have been implicated in adverse reactions. Computation of a list of formulations of bronchodilators, antihistamines, and antibiotics that are free of such additives.**

***Results*—A total of 118 out of 120 pharmaceutical companies supplied the data requested. In all, 2204 drug formulations were analysed and found to contain 419 different additives, of which 52 were colourings and preservatives that have been implicated in adverse reactions; 930 formulations contained such an additive. Tartrazine was the fourth most commonly occurring colouring, being present in 124 drug formulations.**

***Conclusion*—Many drugs contain additives that help to identify them and prolong their shelf life but are implicated in adverse reactions in some people. Some form of labelling of drug additives would enable these people to avoid drugs containing such additives.**

Introduction

Many additives are used in drugs by the pharmaceutical industry for a variety of reasons, including improved identification and stability. Although adverse reactions to drugs have been reported and investigated for many years, adverse reactions to drug additives such as colourings and preservatives have been reported only over the past 30 years.[1-4] Some of the colourings and preservatives that are added to drugs are also added to foods, and various adverse reactions have been attributed to them, although the validity of reports has been questioned.[5] Colourings, however, have been reported to cause urticaria[6-10] and preservatives, such as sulphites, to cause asthma.[11-13] There is little evidence that food or drug additives cause hyperactivity in children[14] despite popular perceptions and the results of several studies.[15-18]

The prevalence of adverse reactions to food additives

is uncertain, but a survey in the United Kingdom in 1987 suggested that at least 0·01-0·23% of the population is affected.[19] To help doctors to prescribe suitable drugs for patients proved or suspected to be intolerant to colourings or preservatives, or both, we conducted a survey of drug additives with the cooperation of most drug manufacturers in the United Kingdom.

Methods

We posted a standard letter to drug manufacturers that requested details of their drug formulations with special regard to the content of colourings and preservatives. The information was entered into a database, and the data were analysed with regard to the additives most commonly reported to cause adverse reactions. The box lists the additives included in this definition; the colourings were mostly those previously derived from coal tar (for example, tartrazine), and the preservatives included antioxidants (for example, benzoates, sulphites, butylated hydroxyanisole, and butylated hydroxytoluene). If evidence to implicate an additive in an adverse reaction was inconclusive for the purposes of the survey we considered that it could cause such a reaction.

Drug additives that have been reported to cause adverse reactions

Colourings

- Amaranth
- Black PN
- Blue (colour index Nos 12196 and 16383*)
- Brilliant blue FCF
- Brown FK
- Brown HT
- Brown (colour index No 18285)*
- Buff (colour index No 17175)*
- Carmoisine
- Disperse blues
- Disperse pinks
- Erythrosine BS
- Green S
- Indigo Carmine
- Patent blue V
- Ponceau 4R
- Quinoline yellow
- Red 2G
- Sunset yellow FCF
- Tartrazine
- Yellow 2G
- Various commercial mixes containing the above colourings

Preservatives and antioxidants

- Benzoates
- Sulphites
- Butylated hydroxyanisole
- Butylated hydroxytoluene

*Not permitted food additives.

Results

A total of 120 pharmaceutical manufacturers were contacted during 1988, and only two would not supply the information requested. The manufacturers gave us permission to publish information on drug additives in named drugs in the categories of the *British National Formulary* (see table II). In all, the drugs contained 419 different additives. Of these, 52 colourings and preservatives were categorised as having been implicated in adverse reactions, leaving 367 for which no evidence of adverse effects existed.

Table I gives the prevalence in 930 drug formulations of some of the colourings and preservatives that have been implicated in adverse reactions. Erythrosine was the commonest colouring, being added to 191 drugs; tartrazine was added to 124, and benzoates occurred in 290. Table II gives the additives in drugs according to the categories of the *British National Formulary*. Central nervous system agents were the drugs that most commonly contained a colouring or preservative, or both, that had been implicated in adverse reactions.

Of the 2204 drug formulations analysed, 532 contained a colouring, 281 a preservative, and 117 both a colouring and a preservative that had been implicated in adverse reactions. Table III lists formulations of bronchodilators, antihistamines, and antibiotics that are free of such colourings and preservatives. Data were not obtained on the amount of a particular additive in each drug; available data, however, suggest that some tablets contain up to 2·7 mg of tartrazine.[20]

TABLE I—*Number of drug formulations that contained various colourings and preservatives that have been implicated in adverse reactions*

	No (n=930)
Colouring	
Erythrosine	191
Sunset yellow	187
Indigo carmine	142
Quinoline yellow	123
Tartrazine	124
Amaranth	97
Ponceau 4R	95
Preservatives	
Benzoates	290
Parabens	95
Sulphites	51
Butylated hydroxyanisole and butylated hydroxytoluene	13

TABLE II—*Number of drug formulations (n=930) with colourings or preservatives, or both, that have been implicated in adverse reactions according to categories in British National Formulary*

Category of drug	With preservative implicated in adverse reactions	With colouring implicated in adverse reactions	With colourings and preservatives implicated in adverse reactions
Gastrointestinal	32	32	11
Cardiovascular	13	110	5
Respiratory	43	40	27
Neurological	33	141	28
Infections	35	58	28
Endocrine	10	11	3
Obstetrics, gynaecology, and urinary tract	2	4	
Malignancy	7	8	
Nutrition and blood	25	58	10
Musculoskeletal and joint	6	41	4
Eye	3	2	
Ear, nose, and throat	7	10	
Skin	46	16	1
Immunological			
Anaesthesia	19	1	
Total	281	532	117

Discussion

Many drug additives have important functions. Bright and stable colouring of drugs is important because patients who take a variety of drugs need to be able to identify them to minimise the risk of accidental overdose and to help identification of drugs in people who have deliberately taken an overdose. Often the most stable and strong colourings are those implicated in adverse reactions, and many of these were previously derived from coal tar.[21] Some colourings that occur naturally are available commercially, but generally, with the exception of iron and titanium oxides, they are less powerful colourants. Also, some of the colourings used to replace those implicated in adverse reactions may not be completely inert.

Clearly, drugs need to have a reasonable shelf life, and therefore many drugs, especially liquid formulations, contain benzoates and to a lesser extent sulphites. Sulphites can cause bronchospasm in some people with asthma (probably by liberating sulphur dioxide), and once the presence of sulphite in a drug formulation has been identified such people can avoid the formulation.

Several drug manufacturers informed us that tartrazine and some other related colourings have been replaced over the past five years; our survey, however, shows that they are still in widespread use. Comparisons with drug formulations in Europe are limited to data from a recent survey in Switzerland, from which it seems that the number of drugs containing azo dyes in that country is similar to that in the United Kingdom; tartrazine is the fourth commonest azo dye in both countries.[22] The data from the present survey are as accurate as possible, but drug formulations are subject to change from time to time, and specific information should be requested from the manufacturer. We did not study generic drug formulations, although they probably contain additives implicated in adverse reactions.

The mechanism of intolerance to colourings and preservatives is unknown. There is little evidence to support an immunological mechanism, but some recent studies support a pharmacological mechanism.[23-25] As no tests of intolerance to additives performed in vitro have been validated such intolerance must be diagnosed clinically and only when symptoms improve when additives are avoided; ideally, blind

TABLE III—*Examples of drugs without colourings or preservatives that have been implicated in adverse reactions*

Proprietary (approved) name of drug	Formulation	Manufacturer
Bronchodilators		
Alupent (orciprenaline)	Tablets	Boehringer Ingelheim
Bricanyl, Bricanyl SA, and Bricanyl compound (terbutaline)	Tablets	Astra
Bronchodil (reproterol)	Tablets	Degussa
CD Franol and CD Franol Plus (ephedrine, theophylline, and phenobarbitone)	Tablets	Sterling-Winthrop
Nuelin and Nuelin SA (theophylline)	Tablets	Riker
Phyllocontin Continus (aminophylline)	Tablets—normal strength, forte, and paediatric	Napp
Sabidal SR 270 (choline theophyllinate)	Tablets	Zyma
Slo-phylline (theophylline (60 and 125 mg)	Capsules	Lipha
Tedral (theophylline and ephedrine)	Tablets	Parke-Davis
Theodrox (aminophylline)	Tablets	Riker
Uniphylline Continus (theophylline)	Tablets	Napp
Volmax (salbutamol)	Tablets	Duncan Flockhart
Antihistamines		
Actidil (triprolidine)	Tablets	Wellcome
Alunex (chlorpheniramine)	Tablets	Steinhard
Dimotane and Dimotane LA (brompheniramine)	Tablets	A H Robins
Fenostil Retard (dimethindene)	Tablets	Zyma
Hismanal (astemizole)	Tablets and suspension	Janssen
Lergoban (diphenylpyraline)	Tablets	Riker
Optimine (azatadine)	Tablets	Kirby-Warrick
Periactin (cyproheptadine)	Tablets	Merck Sharp and Dohme
Piriton (chlorpheniramine)	Tablets	Allen and Hanbury
Primalan (mequitazine)	Tablets	May and Baker
Semprex (acrivastine)	Capsules	Wellcome
Tavegil (clemastine)	Tablets	Sandoz
Thephorin (phenindamine)	Tablets	Sinclair
Tinset (oxatomide)	Tablets	Janssen
Triludan (terfenadine)	Tablets	Merrell Dow
Zirtek (cetririzine)	Tablets	Allen and Hanbury
Antibiotics		
Ambaxin (bacampicillin)	Tablets	Upjohn
Amoxil (amoxycillin)	Tablets	Bencard
Ampilar (ampicillin)	Syrup	Lagap
Augmentin (amoxycillin and clavulanate)	Dispersible tablets and suspension	Beecham
Bacrim (co-trimoxazole)	Tablets	Roche
Baxan (cefadroxil)	Capsules	Bristol-Myers
Calthor (ciclacillin)	Tablets	Ayerst
Ceporex (cephalexin)	Capsules	Glaxo
Ciproxin (ciprofloxacin)	Tablets	Baypharm
Colomycin (colistin)	Tablets	Pharmax
Eradacin (acrosoxacin)	Capsules	Sterling Research
Fasigyn (tinidazole)	Tablets	Pfizer
Flagyl (metronidazole) (200 and 400 mg)	Tablets	May and Baker
Fucidin (sodium fusidate)	Tablets	Leo
Furadantin (nitrofurantoin)	Tablets	Norwich Eaton
Hiprex (hexamine)	Tablets	Riker
Ipral (trimethoprim)	Tablets	Squibb
Kelfizine W (sulfametopyrazine)	Tablets	Farmitalia Carlo Erba
Ladropen (flucloxacillin)	Capsules	Berk
Laratrim (co-trimoxazole)	Tablets	Lagap
Ledermycin (demeclocycline 300 mg)	Capsules	Lederle
Metrolyl (metronidazole)	Tablets	Lagap
Mictral (nalidixic acid)	Granules	Sterling-Winthrop
Minocin (minocycline) (50 mg)	Tablets	Lederle
Miraxid (pivampicillin)	Tablets and paediatric suspension	Fisons
Monotrim (trimethoprim)	Tablets and suspension	Duphar
Myambutol (ethambutol) (400 mg)	Tablets	Lederle
Mynah 200 (ethambutol and isoniazid)	Tablets	Lederle
Negram (nalidixic acid)	Tablets	Sterling Research
Nidazol (metronidazole)	Tablets	Steinhard
Pondocillin (pivampicillin)	Tablets and sachet	Edwin Burgess
Rifater (isoniazid, pyrazinamide, and rifampicin)	Tablets	Merrel Dow
Rimactane (rifampicin) (150 and 300 mg)	Capsules	Ciba-Geigy
Rimactazid 150 (rifampicin and isoniazid)	Tablets	Ciba-Geigy
Selexid (pivmecillinam)	Tablets and suspension	Leo
Septrin (co-trimoxazole)	Tablets—normal strength and forte	Wellcome
Stafoxil (flucloxacillin)	Capsules	Brocades
Syraprim (trimethoprim)	Tablets	Wellcome
Tetralysal 300 (lymecycline)	Tablets	Farmitalia Carlo Erba
Trimogal (trimethoprim)	Tablets	Lagap
Trimopan (trimethoprim)	Tablets	Berk
Uticillin (carfecillin)	Tablets	Beecham
Velosef (cephradine)	Syrup	Squibb
Vibramycin (doxycycline)	Capsules	Pfizer
Zadstat (metronidazole)	Tablets	Lederle
Zinamide (pyrazinamide)	Tablets	Merck Sharp and Dohme

placebo controlled challenges should also be performed.[26]

In 1986 compulsory labelling of foods containing additives was introduced in the United Kingdom, and as a consequence the range and number of foods available without such additives has increased. Whether the prevalence of reactions to food additives has declined since then would be difficult to determine. Compulsory labelling of drugs containing additives exists in some countries and is under consideration in the United Kingdom. It would clearly be useful for doctors to be able to refer to the Association of the British Pharmaceutical Industry's data sheet compendium for guidance when they are prescribing drugs for patients who have been proved or are suspected to be intolerant to colourings or preservatives, or both. Drug manufacturers are usually helpful in supplying information about the additives in their products, but for busy clinicians obtaining information this way can be time consuming.

At present patients presenting with symptoms, such as urticaria, that could be provoked by colourings or preservatives, or both, should avoid additives in drugs and food. When the additive content of a drug is unknown they should take a white tablet formulation as these are commonly free of colourings and preservatives and usually can be crushed and added to food for administration to children.

IP, EY, and NS were supported as part of a grant from the Ministry of Agriculture, Fisheries, and Food.

1 Lockey SD. Allergic reactions to F D and C yellow No 5 tartrazine, an aniline dye used as a coloring and identifying agent in various steroids. *Ann Allergy* 1959;**17**:71.
2 Jenkins P, Michelson R, Emerson PA. Adverse drug reaction to sunset yellow in rifampicin/isoniazid tablet. *Lancet* 1982;ii:385.
3 Nagel JE, Fuscaldo JT, Fireman P. Paraben allergy. *JAMA* 1977;**237**:1594.
4 Reisman RE. Delayed hypersensitivity to methiolate preservative. *Journal of Allergy* 1969;**43**:245.
5 Simon RA. Adverse reactions to drug additives. *J Allergy Clin Immunol* 1984;**74**:623-30.
6 Michaelsson G, Juhlin L. Urticaria induced by preservatives and dye additives in food and drugs. *Br J Dermatol* 1973;**88**:525-32.
7 Supramanium G, Warner JO. Artificial food additive intolerance in patients with angio-oedema and urticaria. *Lancet* 1986;ii:907-9.
8 Settipane GA, Chafee FH, Postman M, Levine MI. Significance of tartrazine sensitivity in chronic urticaria of unknown etiology. *J Allergy Clin Immunol* 1976;**57**:541-6.
9 Ros A, Juhlin L, Michaelsson G. A follow-up study of patients with recurrent urticaria and hypersensitivity to aspirin, benzoates and azo dyes. *Br J Dermatol* 1976;**95**:19-24.
10 Warin RP, Smith RJ. Role of tartrazine in chronic urticaria. *Br Med J* 1982;**284**:1443-4.
11 Stevenson DD, Simon RA. Sensitivity to ingested metabisulphites in asthmatic subjects. *J Allergy Clin Immunol* 1981;**68**:26-32.
12 Weber RW, Hoffman M, Raine Jr DA, Nelson HS. Incidence of bronchoconstriction due to aspirin, azo dyes, non-azo dyes, and preservatives in a population of perinial asthmatics. *J Allergy Clin Immunol* 1979;**64**:32-7.
13 Beasley R, Rafferty P, Holgate ST. Adverse reactions to the non-drug constituents of nebuliser solutions. *Br J Clin Pharmacol* 1988;**25**:283-7.
14 Taylor EA. *The overactive child.* Oxford: Blackwell, 1986.
15 Feingold BF. *Why your child is hyperactive.* New York: Random House, 1975.
16 Egger J, Carter CM, Graham PJ, Gumley D, Soothill JF. Controlled trial of oligoantigenic treatment in the hyperkinetic syndrome. *Lancet* 1985;i:540-5.
17 David TJ. Reactions to dietary tartrazine. *Arch Dis Child* 1987;**62**:119-22.
18 Pollock I, Warner JO. The effect of artificial food colours on childhood behaviour. *Arch Dis Child* (in press).
19 Young E, Patel S, Stoneham M, Rona R, Wilkinson JD. The prevalence of reaction to food additives in a survey population. *J R Coll Physicians Lond* 1987;**21**:241-7.
20 Smith LJ, Slavin RG. Drugs containing tartrazine dye. *J Allergy Clin Immunol* 1976;**58**:456-70.
21 Hess H, Schrank J. Colouration of pharmaceuticals—possibilities and technical problems. *Acta Pharm Tech* 1979;**25**(suppl 8):77-87.
22 Kolly M, Pecoud A, Frei PC. Additives contained in drug formulations most frequently prescribed in Switzerland. *Ann Allergy* 1988;**62**:21-5.
23 Murdoch RD, Lessof MH, Pollock I, Young E. Effects of food additives on leukocyte histamine release in normal and urticarial subjects. *J R Coll Physicians Lond* 1987;**21**:251-6.
24 Murdoch RD, Pollock I, Naeem S. Tartrazine induced histamine release in vivo in normal subjects. *J R Coll Physicians Lond* 1987;**21**:257-61.
25 Murdoch RD, Pollock I, Young E, Lessof MH. Food additive-induced urticaria: studies of mediator release during provocation testing. *J R Coll Physicians Lond* 1987;**21**:262-6.
26 Warner JO. Artificial food additive intolerance: fact or fiction? In: Dobbing J, ed. *Food intolerance.* London: Baillière and Tindall, 1987:133-47.

(Accepted 11 July 1989)