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.

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Survey of colourings and preservatives in drugs

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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 urticaria⁶⁻¹⁰ and preservatives, such as sulphites, to cause asthma.¹¹⁻¹³ There is little evidence that food or drug additives cause hyperactivity in children¹⁴ despite popular perceptions and the results of several studies.¹⁵⁻¹⁸

The prevalence of adverse reactions to food additives

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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.

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

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

	No (n=930)
<i>Colouring</i>	
Erythrosine	191
Sunset yellow	187
Indigo carmine	142
Quinoline yellow	123
Tartrazine	124
Amaranth	97
Ponceau 4R	95
<i>Preservatives</i>	
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

Drug additives that have been reported to cause adverse reactions

Colourings

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

Preservatives and antioxidants

Benzoates	Butylated hydroxyanisole
Sulphites	Butylated hydroxytoluene

*Not permitted food additives.

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

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

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