Polyglandular autoimmune syndrome: current concepts

Jeffrey Meyerson, MB, ChB
Emilio E. Lechuga-Gomez, MD
Pierluigi E. Bigazzi, MD
Paul G. Walfish, MD, FRCPC, FACP

The polyglandular autoimmune syndrome (PGAS) is characterized by the association of two or more endocrine disorders that are mediated by autoimmune mechanisms and usually lead to a hypofunctional state. In this review we classify the various types of PGAS and discuss their clinical features and the pathophysiologic autoimmune mechanisms that are thought to play an important role. Circulating organ- and cell-specific autoantibodies are frequently detected in patients with the syndrome and may be a marker of future organ failure. PGAS should be considered in patients with one or more of the disorders constituting the syndrome; this should facilitate early diagnosis and perhaps even prevention of other components of the disease. Early recognition and replacement therapy can be life-saving, particularly when there is adrenal or thyroid insufficiency.

Les syndromes polyglandulaires auto-immuns (SPGA) associent des troubles d'au moins deux sortes de glandes endocrines qui sont affectées par des mécanismes auto-immuns, évoluant le plus souvent vers l'insuffisance. On passe en revue les divers syndromes, leurs manifestations cliniques et leurs mécanismes auto-immuns présumés. Les malades sont souvent porteurs d'auto-anticorps spécifiques à l'égard de certains organes ou de certaines cellules; la présence de tels anticorps permet à l'occasion de prévoir la survenue ultérieure d'une insuffisance glandulaire. La présence de l'une quelconque des composantes de ces syndromes doit faire soupçonner l'existence d'un SPGA. On sera ainsi à même de reconnaître en temps utile une nouvelle composante, sinon de la prévenir parfois, et de lui opposer une thérapeutique précoce de remplacement. Celle-ci, surtout devant une insuffisance surrenalienne ou thyroïdienne, peut sauver la vie du malade.

Early in the study of endocrine disease it was noted that some patients could present with or eventually manifest functional failure of more than one endocrine gland. Pathological hallmarks of the affected glands were gradual destruction of epithelial cells, lymphoid infiltration and replacement of normal tissue by fibrous tissue. Several causes were considered, including glandular failure secondary to pituitary cachexia, with a deficiency of pituitary trophic hormones. In 1908 Claude and Gourgerot hypothesized that similar processes could involve each gland separately and independently of the others. A few years later Falta modified this concept and emphasized milder forms of the syndrome, in which some glands presented partial or incomplete atrophy. In 1926 Schmidt noted the relation between adrenal and thyroid failure, with or without diabetes mellitus,
which has now become a syndrome not infrequently recognized. During the past several decades there has been an increased awareness of the strong relation between autoimmunity and endocrine disorders.6-10 The autoimmune origin of Hashimoto’s thyroiditis and Graves’ disease has been well documented.6-10 The relation between receptor antibodies and endocrine disorders has also been recognized.11 There have been several reports on the polyendocrine failure syndrome, and an autoimmune origin for this syndrome has been proposed.11,12

Clinical classification

According to the classification of Neufeld and Blizzard13 there are three types of polyglandular autoimmune syndrome (PGAS). Type I is a syndrome of candidiasis, hypoparathyroidism and adrenal insufficiency. Type II involves one or more of adrenal insufficiency, thyroid autoimmune disease and insulin-dependent diabetes mellitus (IDDM). Type III involves restricted polyendocrine associations: (a) thyroid autoimmune disease and IDDM; (b) thyroid autoimmune disease and pernicious anemia; and (c) thyroid autoimmune disease as well as one or more of vitiligo, alopecia and organ-specific autoimmune disease not in categories (a) and (b).

PGAS type I

PGAS type I affects males and females with equal frequency. The onset of this variant is usually during childhood; a few patients are affected after the age of 10 years.14 Although the triad of candidiasis, hypoparathyroidism and adrenal insufficiency is present in many patients, most are initially evaluated for symptoms related to mucocutaneous candidiasis, which often precedes the development of the other two components.

In females with PGAS there is typically a history of regular menstrual periods and even fertility in early adulthood. However, the onset of premature secondary amenorrhea is often sudden and is associated with serum hypergonadotropism (the serum level of follicle-stimulating hormone is elevated to a greater degree than is the level of luteinizing hormone) and a reduced serum estrogen level.15 Ovarian failure with hypergonadotropic secondary amenorrhea has been noted most commonly with PGAS type I, but it may also occur in patients with the type II variant,14,16,17 and there is frequently overlap between the various forms of PGAS.

Malabsorption syndrome, chronic active hepatitis, alopecia, primary gonadal failure, defective dental enamel formation and pernicious anemia have also been noted in association with PGAS type I. IDDM and thyroid disease are infrequently associated.13

PGAS type II

The main features of PGAS type II were originally described by Schmidt3 as coexistent adrenal and thyroid failure. The essential determinant of type II is adrenal insufficiency, but patients may present with symptoms of IDDM several years before the adrenal insufficiency appears.18 Females are three times as often affected as males, and the onset is usually in adulthood.13 Irvine19 reported that 69% of patients with autoimmune adrenitis have concomitant autoimmune thyroid disease, with Graves’ disease and primary atrophic hypothyroidism being more common than goitrous autoimmune thyroiditis. Irvine found that 52% of patients initially present with IDDM. Gonadal failure, vitiligo, alopecia and hypophysisitis are less commonly associated.11,13

Ovarian failure with hypergonadotropic secondary amenorrhea has been observed to typically precede the adrenal insufficiency by several years.20 The presence of antiovary and antitesticular steroid-cell antibodies, which also react with adrenal cortical cells, has been noted in this condition.21 Vitiligo has been reported in less than 5% of patients with PGAS type II.17,22 Autoantibodies to melanin-producing cells have been suggested as the cause of the vitiligo.17

PGAS type III

PGAS type III has been defined as autoimmune thyroid disease in association with diabetes mellitus, pernicious anemia, vitiligo, alopecia or hepatic autoimmune disease but not with adrenal involvement.13 Many patients, however, later manifest adrenal insufficiency, and their condition may then be reclassified as PGAS type II.13

Humoral autoimmunity

Although several authors postulated an interrelation between polyglandular failure and autoimmunity, Roitt and colleagues23 and Doniach and associates24 first demonstrated the relation between antithyroglobulin antibodies and Hashimoto’s goitrous thyroiditis. Rose and Witebsky25 induced thyroiditis in rabbits by injecting them with thyroid gland homogenates, and a long-acting thyroid stimulator was demonstrated in the serum of a patient with Graves’ thyrotoxicosis.26 This was later shown to be a thyroid-stimulating hormone (TSH) receptor-stimulating antibody.4-7

Subsequently many organ-specific humoral antibodies to endocrine organs were demonstrated.4,11,27 Most patients with autoimmune thyroiditis have circulating autoantibodies capable of reacting in vitro with thyroglobulin, “microsomal” antigen and other cell surface autoantigens.28 Autoantibodies to thyroglobulin antigen have been detected by a standard commercial hemagglutina-
tion method in the serum of 30% to 40% of patients with autoimmune thyroiditis or untreated Graves’ disease and 50% to 60% of patients with primary myxedema.6,7 Autoantibodies to thyroid microsomal antigen, recently shown to be identical to thyroid peroxidase antigen, are detected with a very sensitive enzyme-linked immunosorbent assay (ELISA) and show a highly significant correlation with results obtained with standard hemagglutination testing; these autoantibodies are found in most patients with Hashimoto’s disease, up to 85% of patients with Graves’ disease and many patients with PGAS type II.28 These antibodies are complement fixing and are also cytotoxic to thyroid cells that have been cultured and altered by enzyme pretreatment.9 A complete correlation has been demonstrated between complement-mediated antibody-dependent cytotoxicity and cell surface immunofluorescence on cells freshly dispersed with trypsin.28 This finding supports the possibility that antithyroidal cytotoxic antibodies are identical to thyroid membrane antibodies. Alternatively, the latter may interact with thyroid epithelial cells and initiate antibody-dependent cell-mediated cytotoxicity (ADCC), which is further discussed in the section on cell-mediated autoimmunity.

In Addison’s disease anti-adrenal-cortex antibodies have been demonstrated,11,29 and steroid-cell antibodies that cross-react with ovarian granulosa cells as well as adrenal cortex have been reported in some cases of premature primary ovarian failure.30 Circulating adrenal antibodies are present in 20% to 80% of patients with Addison’s disease.29 They are usually present in low titres and are detected more frequently in female than in male patients and in those with disease of short duration or of onset at a very early age.29 However, there is no correlation between titre, age at time of diagnosis and duration of disease.29 The antibodies occur with relatively high frequency in idiopathic hypoparathyroidism (30%) and occasionally in patients with diabetes and thyroid disorders.29 They are rare in control populations (occurring in less than 0.1%) and have not been detected in a matched control series.29 Other autoantibodies (i.e., to thyroglobulin and thyroid microsomal antigen, gastric parietal cells, interstitial cells of the ovary and testis, intrinsic factor, parathyroid cells and islet cells) have been demonstrated in patients with Addison’s disease.29 Of particular interest are the serum antibodies that react with steroid-producing cells of the ovary and testis. Serum from patients with Addison’s disease reacts by indirect immunofluorescence not only with the theca interna cells, interstitial cells and corpus luteum cells of the ovary but also with the interstitial cells of the testis and with placental trophoblasts.29

Although previously most results supporting an autoimmune origin of endocrine disease were obtained in thyroid disease,31-38 cytotoxic autoantibodies to pancreatic β-cells in the serum of patients with IDDM have been observed, initially by Dobersen and coworkers,29 and subsequently there has been increasing evidence that IDDM is also a chronic autoimmune disease.40 In this disease several immunologic abnormalities may precede the development of overt disease. Anticytoplasmic islet cell antibodies have been found in 70% of patients with IDDM of recent onset and in a similar proportion of those with prediabetes.41 Patients with diabetes mellitus and their first-degree relatives may have additional serologic abnormalities, such as antibodies to thyroglobulin, antibodies to thyroid microsomal antigens and single-stranded DNA. Such additional abnormalities appear to be associated with an increased prevalence of autoimmune disease.42 Since the prodromal stage can last more than a decade and since most of those with islet cell antibodies have marked impairment of first-phase insulin secretion after intravenous administration of glucose, it is likely that overt diabetes mellitus will develop in most people with these antibodies.42

Autoantibodies that immunoprecipitate insulin have also been noted before the onset of type I diabetes. In a collaborative study such antibodies were found in approximately 30% of those in whom type I diabetes later developed; 80% of those with autoantibodies to insulin also had islet-cell antibodies.43 Their true significance as markers for the development of type I diabetes remains unclear, but insulin antibodies appear to have prognostic importance.42,43

Autoantibodies to vasopressin cells in idiopathic diabetes insipidus have been reported by Scherbaum and Bottazzo.44 Bottazzo and collaborators45 have also demonstrated autoantibodies to prolactin-producing cells of the human pituitary. In addition, antibodies to melanocytes,17 spermatozoa, secretin-producing cells, gastrin-inhibitory-peptide-producing cells, pancreatic α-cells, parathyroid chief cells and somatostatin-producing cells have been reported.11 Their significance in autoimmune-mediated cellular dysfunction has not been fully elucidated.

The characterization of Graves’ disease as an autoimmune disorder is based largely on the finding that serum of patients with the disease usually contains one or more autoantibodies to normal constituents of thyroid tissue, such as thyroglobulin, microsomal protein and the TSH receptor. The hyperthyroidism characterizing the disease is attributed to the thyroid-stimulating properties of the antibody to the TSH receptor.43,45 TSH receptor-stimulating antibodies mimic the action of TSH by stimulating production of adenosine 3’;5’-cyclic monophosphate (cyclic AMP), radioactive iodine uptake and colloid droplet formation, as well as increased thyroid epithelial growth, as shown by the enhanced uptake of tritiated thymidine into DNA; probably the antibodies and TSH compete for the same binding site on the TSH receptor molecule.36,37 Antibodies that may block the action of the TSH-receptor stimulator by binding to the receptor (TSH-binding-inhibitor immunoglobulin) or by direct inactivation of the
stimulating antibody may induce hypothyroidism. Drexhage and colleagues have observed serum antibodies that stimulate growth at a site different from the TSH receptor, to induce goitre without hyperthyroidism. These thyroid growth-promoting autoantibodies may be a distinct population of thyroid-stimulating antibodies and may be present in the circulation of patients with autoimmune thyroiditis. Graves' disease and non-toxic goitre. Although such autoantibodies may play a role in goitre formation their precise properties remain to be characterized and distinguished from those of other growth factors such as TSH-receptor-stimulating immunoglobulins, insulin growth factors and epidemial growth factors.

Although Graves' ophthalmopathy is almost certainly immunologically mediated, neither the precise mechanism(s) producing eye tissue damage nor the target antigen(s) of the autoimmune reaction is known. The eye muscle appears most likely to be involved, since its fibres are infiltrated with immunocompetent cells. Circulating antibodies to both soluble and membrane-derived eye muscle antigens have been detected in patients with Graves' ophthalmopathy by means of an ELISA and, more recently, indirect immunofluorescence. The precise role of these antibodies, however, remains unclear. Recent studies suggest that they are cytotoxic only in association with ADCC, unlike the thyroid microsomal antibody, which is cytotoxic both directly and in association with ADCC. However, the detection of eye muscle antibodies in some hyperthyroid patients before the development of overt eye disease as well as in the occasional patient with type I diabetes mellitus and in an apparently healthy first-degree relative of a patient with ophthalmopathy suggests that the antibodies may be detected in subjects predisposed to ophthalmopathy before the onset of eye disease.

Since there is also lymphocytic infiltration in the periorbital and orbital connective tissue, autoimmune reactions may occur against components of the orbital connective tissue such as fibroblasts, endothelial cells and glycosaminoglycans. Recent evidence suggests that fibroblasts may be an important target for the TSH receptor autoantibodies present in patients with Graves' disease who have ophthalmopathy. This supports the concept that the ophthalmopathy may be due to an autoimmune reaction involving antigens found in connective tissue and shared by thyroid and orbital tissues. Whatever the antigen, such antibodies may be useful as markers of ophthalmopathy in autoimmune thyroid disease. Therapeutic maneuvers to prevent the development of ophthalmopathy in such patients, such as using thiouracils or immunosuppressive agents, may thus become possible, but further evidence to support this rationale is required.

Blocking antibodies have also been reported in other diseases thought to be mediated by autoimmune mechanisms. For example, parietal cell antibodies block the access of gastrin and interfere with the action of carbonic anhydrase, which leads to decreased gastric acid secretion and acetylcholine receptor antibodies are present in myasthenia gravis.

Special attention has been given in the last few years to the peripheral action of insulin receptor antibodies. The tissue insulin receptors can be blocked by circulating autoantibodies, as in insulin-resistant diabetes mellitus related to acanthosis nigricans. These antibodies may also be able to stimulate the insulin receptor to mimic the action of insulin and induce hypoglycemia, as in the case reported by Taylor and associates. Insulin receptor antibodies may also have a physiologic role in IDDM. Maron and coworkers reported their presence in the serum of 10 of 22 patients with the disease before treatment with exogenous insulin, and anti-insulin-receptor antibodies developed during treatment with human or pork insulin in 2 of 5 patients with negative results initially.

Human monoclonal autoantibodies that react with several endocrine organs, including the pituitary gland, have been reported. This finding suggests that the simultaneous occurrence of antibodies that react with multiple human organs may account for PGAS or other syndromes of multiple organ insufficiency and that the various affinities of the monoclonal antibodies may account for the observed variation in severity and clinical manifestations.

Cell-mediated autoimmunity

Lymphocytes from patients with Hashimoto's thyroiditis, Graves' disease or IDDM produce migration inhibition factor (MIF) after stimulation with thyroid or pancreatic antigens. However, routine MIF testing in patients with PGAS has rarely been done. Edmonds and collaborators reported that a patient with adrenitis, thyroiditis and oophoritis had positive results of MIF tests for all three affected endocrine organs, even in the absence of circulating organ-specific autoantibodies, which suggests that cell-mediated autoimmune mechanisms may be important in the development of PGAS.

Most patients with autoimmune thyroiditis have delayed-type hypersensitivity responses to thyroid autoantigens, detectable by various procedures. In-vitro tests have shown that lymphocytes from patients with autoimmune thyroiditis produced lymphokines after stimulation with thyroid antigens. Inhibition of lymphocyte migration has been observed in 66% of patients when crude thyroid extract was used, compared with 40% when purified thyroglobulin was used and 27% when thyroid microsomal antigen was used. In other studies migration of lymphocytes obtained from patients with autoimmune thyroiditis was inhibited after the cells were stimulated with
thyroid microsomal antigen but not after they were incubated with thyroglobulin.28

A direct cytotoxic effect of lymphocytes from patients with autoimmune thyroiditis has been reported by several investigators.26 Activity of natural killer (NK) cells against thyroid cells is present in patients with Hashimoto’s disease but is not significantly different from that in healthy people.28 This does not exclude a possible role of NK cells as a mechanism of thyroid cell destruction in Hashimoto’s thyroiditis, but it indicates that other mechanisms, such as ADCC, may have a more important role. In Addison’s disease as well, up to 80% of patients may have cell-mediated immune reactions to adrenal antigens, as determined with the lymphocyte migration test.29 Antibody-dependent cellular cytotoxicity is a combination of humoral and cellular immunity that requires the binding of specific antibodies to their target cells and the attachment of nonsensitized lymphoreticular cells to the Fc (crystallizable fragment) region of these antibodies, which leads to target cell death through an extracellular, nonphagocytic mechanism.28 Among the cells involved are lymphocytes that have Fc receptors and do not belong to either the mature T-cell or B-cell population. Antibody-dependent cell-mediated cytotoxicity and NK-cell activity have been reported to play an important role in the immune mechanism of Hashimoto’s thyroiditis.30 Finally, a microcytotoxicity assay for thyroid-specific antibody-dependent cellular cytotoxicity, developed using human thyroid epithelial cells as targets, has confirmed that serum from patients with Hashimoto’s thyroiditis has significantly more cytotoxic activity than serum from healthy people.28

There has been extensive research on the possible reduction in suppressor T-cell function that could lead to an immunoregulatory defect that permits a predominance of helper T cells. Such an abnormality has been seen in T-lymphocyte subsets in peripheral blood from patients with autoimmune thyroid disease or diabetes mellitus.31,58,60

Despite the intense interest in humoral immunity it is unlikely that islet cell or insulin antibodies are the major determinant of β-cell destruction in the development of type I diabetes mellitus. Islet cell antibodies may not be specific for β-cells, and there is considerable recent evidence of a significant role for T lymphocytes — in particular, the activated T lymphocytes that express the DR or Ia antigen (HLA class II molecule) on their surface.40 Elevation of circulating levels of Ia-positive cells has been shown to precede the development of type I diabetes mellitus,41 and a similar increase in Ia-positive T cells has been reported in DR3-associated autoimmune diseases such as Graves’ disease62 and Addison’s disease.63

**Genetic predisposition and pathogenesis**

A strong relation has been documented between the presence of certain HLA genes in the major histocompatibility complex and the presence of various endocrine diseases.64-66 This finding supports the involvement of genetic factors in PGAS. The D region of the HLA antigens is characterized by at least three subloci (i.e., DP, DQ and DR), each of which codes for at least two polypeptide chains. Two of the genes produce glycopeptides that combine in a two-chain molecule that affects interactions between T cells, B cells and macrophages to determine whether suppressor or helper T-cell responses to a given antigen will occur.67 HLA-D subgroup DR3 and HLA-B8 have been found to be associated with PGAS type II.67 It appears that susceptibility to the syndrome rather than the specific illness is inherited, so that one may find family members with one or more of the end-organ endocrine defects. A degree of genetic polymorphism in the expression of the HLA-DR antigen subgroup may also account for this variability among families in the expression of PGAS type II.

Finally, PGAS type II appears to follow an autosomal dominant mode of inheritance (with variable penetrance), whereas PGAS type I is probably inherited as an autosomal recessive condition and does not appear to have an HLA association.67

An attractive theory proposes that patients with PGAS have certain susceptibility genes that are closely linked to an HLA haplotype, thereby predisposing to a defect in immune control.67,68 Environmental triggering factors,69 such as viral infections or stress-precipitating events, could also be involved in the development of a defect in suppressor T-lymphocyte function, with subsequent proliferation of the appropriate clone of autoreactive helper T lymphocytes and cytotoxic T cells, which would in turn prolong or perpetuate a cell-mediated and humoral autoimmune disease.73

Alternatively, perturbations in the idiotype/anti-idiotype network may be involved in autoimmune diseases.7,71,68 An antibody response to an antigen generates an idiotype that distinguishes one immunoglobulin from another of the same allotype. Each idiotype may also be recognized by the immune system as being antigenic and, in turn, will generate a corresponding anti-idiotype. Not only circulating antibodies but also B cells that produce antibodies carry idiotypes on their surface. Immuno regulatory T cells carry similar (but not identical) determinants. The introduction of an antigen stimulates the production of idiotype-bearing antibodies, with anti-idiotypic modulation by idiotype-bearing T and B cells to reach a new dynamic equilibrium.

**Clinical significance of autoantibodies**

Discrepancies may occur between the clinical expression of PGAS and the presence or absence of
positive results of organ-specific serologic testing. Thus, positive autoimmune serologic results may precede the onset of clinical disease; this is most likely when islet cell or adrenal antibodies are present. There is an unexpectedly high frequency of organ-specific antibodies in PGAS in the absence of clinically expressed adrenalitis (with adrenal antibodies) or autoimmune diabetes mellitus (with islet cell antibodies). Although actuarial data are not available to substantiate clinical predictions, preliminary follow-up studies suggest that the presence of unusual organ antibodies such as islet cell antibodies and adrenal antibodies may also help to diagnose the disease. This is in striking contrast to observations based on thyroid or gastric antibodies in population studies, which suggest that only about 10% of serologically positive people will later manifest clinical disease. Refined endocrine function tests can now be performed in the follow-up of patients suspected to have PGAS, and first-degree relatives could be screened every few years with standard tests for glycemia and for thyroid and adrenal dysfunction in the search for early or partial deficiency, which may indicate future glandular failure. The evaluation of patients with idiopathic (autoimmune) adrenal insufficiency should include determination of serum levels of thyroxine, TSH and postprandial glucose, since as many as 45% of such patients eventually manifest at least one associated endocrinopathy. Similarly, the determination of serum autoantibodies could signal the possibility of future organ failure in patients with PGAS.

In conclusion, classic polyglandular syndromes are centred on the two most severe disorders, idiopathic hyperparathyroidism and Addison’s disease, or autoimmune adrenalitis. However, the thyroid gland remains most commonly involved in autoimmunity in Graves’ thyrotoxicosis, with its incomplete variants, in endocrine exophthalmos, and in sporadic nodular goitre. It is important to note that several or all of these conditions may evolve in the same patient in the course of a lifetime.

In the complicated polyendocrine disorders, other associations between endocrine hyperfunction and hypofunction may exist. Undiscovered relations with Cushing’s syndrome are now suspected, and one family has been described in which the mother had polyglandular adenomatosis, thus far unrelated to autoimmunity, whereas several of her offspring had clear evidence of the adrenalitis–thyroiditis syndrome, with the corresponding antibodies in their serum. Theoretically, PGAS should be considered in any patient with one expressed endocrine disease who shows serologic reactivity with another organ. This expanded view will facilitate the early diagnosis and treatment of patients with PGAS. Such considerations may also help widen our understanding of the interplay of certain nonendocrine diseases that appear to be more common in patients with endocrine disease.

Summary

PGAS has become an increasingly recognized clinical entity in endocrinology, joining a growing list of disorders likely to be mediated by autoimmune pathogenic mechanisms. Patients with PGAS are currently treated with appropriate replacement therapy for each deficient endocrine organ system. In the future early recognition of these disorders and delineation of their cause and physiopathological features may permit more direct treatment of the underlying autoimmune destructive process, which may prevent progressive dysfunction. Possible future approaches to treatment include avoidance of triggering viral infections and the use of immunosuppressive therapy such as cyclosporine in the management of patients with early-onset PGAS and their relatives who are predisposed to the disease.

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References


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**Prescribing Information**

**IZANTAC INJECTION (ranitidine hydrochloride)**

**PHARMACOLOGICAL CLASSIFICATION**

Histamine H2-receptor antagonist

**INDICATIONS AND USAGE**

IZANTAC injection is indicated for the treatment of duodenal ulcer, benign gastric ulcer, post-operative ulcer, reflux esophagitis, Zollinger-Ellison syndrome and other conditions where reduction of gastric secretion and acid output is desirable. The histamine H2 receptor is the primary site of histamine (HCl) at the parietal cell level, and the prophylaxis of gastrointestinal haemorrhage from stress ulceration in severely ill patients, the prophylaxis of recurrent haemorrhage in patients with bleeding peptic ulcers and before general anaesthesia in patients considered to be at risk of acid aspiration (Mendelson’s syndrome), particularly obstetric patients undergoing Caesarean section.

**CONTRAINDICATIONS**

IZANTAC is contraindicated for patients known to have hypersensitivity to the drug.

**WARNINGS**

Gastric ulcer – Treatment with a histamine H2 antagonist may mask symptoms associated with carcinoma of the stomach and therefore may delay diagnosis of the condition. Accordingly, where gastric ulcer is suspected, the possibility of malignancy should be excluded before therapy with Zantac is instituted.

**PRECAUTIONS**

Use in pregnancy and nursing mothers – The safety of Zantac in the treatment of conditions where a controlled reduction of gastric acid output is required during pregnancy has not been established. Reproduction studies performed in rats and rabbits have revealed no evidence of impaired fertility or harm to the fetus due to Zantac. If the administration of Zantac is considered to be necessary, its use requires that the potential benefits be weighed against possible hazards to the patient and the fetus. However, therapeutic doses of Zantac administered to obstetric patients in labour or undergoing Caesarean section have been without adverse effect on labour, delivery, or subsequent neonatal progress.

Ranitidine is secreted in breast milk in lactating mothers, the clinical significance of this has not been fully evaluated.

Use in impaired renal function – Ranitidine is excreted via the kidney and in the presence of severe renal impairment, plasma levels of ranitidine are increased and prolonged. Accordingly, in the presence of severe renal impairment, clinicians may wish to reduce the dose by one half. Patients with moderate to severe renal impairment (creatinine clearance 15–60 ml/min) may also benefit. For patients with severe renal impairment (creatinine clearance <15 ml/min) blood levels of ranitidine may be excessive and therapeutic drug monitoring is recommended.

**ADVERSE REACTIONS**

Headache, rash, dizziness, constipation, diarrhea and nausea have been reported in a very small proportion of drug-treated patients but these also occurred in patients receiving placebo. A few patients on re-challenge with Zantac have had a recurrence of skin rash, headache or dizziness. Some increases in serum transaminases and gamma-glutamyl transpeptidase have been reported which have returned to normal either on continued treatment or on stopping Zantac. In placebo controlled studies involving nearly 2,500 patients, there was no difference in the incidence of elevations of SGOT and/or SGPT values in the Zantac-treated or placebo-treated groups. Rare cases of hepatitis have been reported but have been transient and no causal relationship has been established.

Anaphylactic reactions (anaphylaxis, urticaria, anaphylactoid oedema, bronchospasm) have been seen rarely following the parenteral and oral administration of Zantac. These reactions have occasionally occurred after a single dose.

Decreases in white blood cell count and platelet count have occurred in a few patients. Other haematological and renal laboratory tests have not revealed any drug related abnormalities.

No clinically significant interference with endocrine or gonadal function has been reported.

A small proportion (1–2%) of patients treated with ranitidine injection experienced lancing or burning at the injection site. This reaction was mild and usually subsided within 10–15 minutes. Headache was experienced by 2.54% of patients receiving ranitidine injection. The majority of these cases were not thought to be treatment-related. In some instances, the headache was thought to be due to over rapid injection of ranitidine, and did not occur on re-challenge with slow intravenous injection. Similarly, some patients experienced nausea after rapid injection of the drug, but on subsequent occasions with slow intravenous injection, experienced no ill-effects.

**SYMPTOMS AND TREATMENT OF OVERDOSE**

No particular problems are expected following over-dosage with Zantac. Symptomatic and supportive therapy should be given as appropriate.

If need be, the drug may be removed from the plasma by haemodialysis.

**DOSEAGE AND ADMINISTRATION**

Adults: Zantac injection may be given either as a slow (over one minute) intravenous injection of 50mg (Many physicians find it convenient to dilute a 2 ml ampoule (50mg) to 25 ml, with Normal Saine and administer over a period of 5 to 10 minutes), which may be repeated every six to eight hours, or as an intravenous infusion at a rate of 50mg per hour for two hours, the infusion may be repeated at six to eight hours intervals.

In the prophylaxis of haemorrhage from stress ulceration in seriously ill patients or the prophylaxis of recurrent haemorrhage in patients bleeding from peptic ulceration, parenteral administration may be continued until oral feeding commences. Patients considered to be at risk may then be treated with Zantac Tablets 150mg twice daily.

In patients considered to be at risk of developing acid aspiration syndrome, Zantac injection 50mg may be given intramuscularly or by slow intravenous injection (see above) 45–60 minutes before induction of general anaesthesia.

Children:

Experience with Zantac in children is limited and has not been fully evaluated in clinical studies – see PRECAUTIONS.

**AVAILABILITY**

Zantac injection is available as 2ml ampoules each containing 50mg ranitidine (as hydrochloride) in 2ml solution for intravenous or intramuscular administration. Packages of 10 ampoules

Zantac tablets are available as white, capsule shaped, film-coated tablets containing ZANTAC 300 on one face and GLAXO on the other, containing 300mg ranitidine (as the hydrochloride) packed in cans containing 28 tablets. Product Monograph available on request.

**REFERENCES**

1. Product Monograph.