PERSPECTIVE

Indocyanine green angiography

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A brief survey of the recent ophthalmic literature underscores a resurgence of interest in indocyanine green angiography (ICGA). This imaging method may be particularly useful for the ophthalmologist, as it provides at least a theoretical advantage for improved imaging of the choroidal circulation when compared with fluorescein angiography. New temporal and spatial technological advances (that is, videoangiography and scanning laser ophthalmoscopy, respectively) are primarily responsible for this renewed interest. Thus, ICGA could become instrumental in elucidating the pathogenetic mechanisms of a variety of diseases processes, as well as serving as a diagnostic and therapeutic tool.

The flurry of recent publications on ICGA, particularly regarding age-related maculopathy (ARM), suggests a new standard of care for the management of patients with this disorder. However, its usefulness in the diagnosis and management of ARM and other disorders is as yet not entirely clear.

Physical properties

The physical and physiological properties of indocyanine green (ICG) were first described by Fox and Wood in 1960, and ICGA has been used extensively by cardiologists since the 1960s for cardiac flow studies.¹ Its first application for fundus angiography was by Kogure and others in 1970 when it was used to visualise the fundus of the owl monkey.²

Fundus fluorescein angiography (FFA) is the accepted standard for imaging the retinal vascular and choroidal circulations. Fluorescein (molecular weight 376) is 80% protein bound; the unbound fluorescein readily escapes through the fenestrations of the choriocapillaris and obscures the details of the underlying choroid. Additional factors which hinder visualisation of the choroid during fluorescein angiography include macular xanthophyll and retinal pigment epithelium which scatter the short wavelength excitation light.³ By contrast, ICG is a tricarbo-cyanine dye (molecular weight 775) which is highly protein bound and does not readily escape from the choriocapillaris. There is a particularly efficient first pass effect in the liver; this limits the recirculation phenomenon which occurs with fluorescein angiography. Indocyanine green absorbs and reflects in the near infrared portion of the spectrum (805 nm and 835 nm, respectively). In this fashion, the retinal pigment epithelium (RPE) is essentially rendered invisible. These characteristics also facilitate visualisation of the choroid through haemorrhage or other pigmentary deposits in the retina or RPE. However, ICG has low fluorescence of only 4% when compared with the total fluorescence of fluorescein.⁴

Early studies

Initial interest and investigations with ICG and other vital dyes occurred during the 1970s. A substantial body of

initial investigations of ICG was published by Flower and Hochheimer, as well as by others.^{4–9} Some of their initial work described a camera adapted with appropriate exciter and barrier filters such that simultaneous ICG and fluorescein angiography could be performed after a single injection of a combined mixture of ICG and fluorescein dyes.⁶ The ICG dosage used in these initial absorption angiography studies tended to be similar to the amount used for cardiac flow studies – that is, 2 mg per kilogram body weight.¹ The early clinical investigators were uniformly disappointed in the lack of usefulness of ICGA in the confirmation of suspected choroidal neovascularisation.^{9–11} ICGA was not a useful guide to laser therapy of choroidal neovascularisation, but appeared to show particular promise in evaluation and monitoring growth of choroidal naevi and choroidal melanomas.^{9–11} In addition, investigators used this new modality to obtain insight into the normal and abnormal appearance of the choroidal circulation.^{9–11–12} These studies were limited in large part by inadequate photographic quality, the resolution of which did not allow visualisation of the choriocapillaris. Also, the motorised shutter cameras had a maximum frequency of exposure of one per 0.7 seconds (average choroidal transit time about 3 seconds). Attempts were made to adapt a 35 mm film camera to a fundus camera in order to improve the temporal resolution for study of the choroidal vascular circulation.^{13–14}

Further technical advances

Recently, improved temporal and spatial resolution led to a renewed interest in ICGA. Tokoro and Hayashi were the first to report the use of the Topcon videoangiography system to improve temporal resolution, and other early clinical reports of ICG videoangiography followed.^{15–17} In 1989, Scheider reported improved spatial resolution by using a scanning laser ophthalmoscope combined with videotape recording.¹⁸ The relative merits of these systems are controversial, particularly their ability to localise and visualise choroidal neovascularisation.¹⁹ There is no firm evidence that binding ICG with human serum albumin before injection improves the quality of ICGA, regardless of the type of camera or scanning laser ophthalmoscope being used.^{20–21} At least two different techniques have been described which allow improved visualisation of the retinal vasculature in the late frames of ICGA, which may be helpful in localising choroidal disorders.^{22–23}

Safety

Initial statistics regarding safety of use of ICG are available from the cardiology and hepatology literature. No untoward effects were seen in over 1000 patients undergoing cardiac function tests as reported by Fox and Wood.¹ In another large series of over 240 000 intravenous injections of ICG, four patients experienced adverse reactions – one

with urticaria and three with anaphylactic reactions (one resulting in death).²⁴ Inadvertent subcutaneous injection may cause discoloration of the skin for several weeks.¹¹

In preparation for intravenous injection, ICG is dissolved in the accompanying aqueous solvent; this contains sodium iodide to prevent recrystallisation. Thus, known iodine allergy and previous allergic reaction to ICG are the only absolute contraindications to its use. Other strong relative contraindications include an allergic diathesis, liver disease, haemodialysis, and pregnancy.

Apparent idiosyncratic anaphylactic reactions have been reported in the ophthalmic literature.²⁵ Recent cumulative reports of large series of patients undergoing ICGA have been instrumental in re-establishing the safety of this procedure. Two recent publications document a total of 5697 ICG angiograms for ophthalmic imaging, and show a paucity of adverse reactions. Hope-Ross and co-workers showed three (0.15%) mild adverse reactions (nausea, vomiting, sneezing), four (0.2%) moderate adverse reactions (urticaria), and only one (0.05%) severe adverse reaction (decreased blood pressure without evidence of anaphylaxis).²⁶ The occurrence of adverse side effects in the Asian population is similar.²⁷ No deaths have been reported in the ophthalmic literature.

Age-related maculopathy

The physical properties of ICG might make it potentially advantageous for the assessment and management of age-related maculopathy (ARM). However, our understanding of the theoretical advantages does not necessarily correlate with the information obtained in the clinical setting.

To date, there has been only one report of the ICG fluorescence characteristics of drusen.²⁸ In this study, 37 patients with juvenile and senile drusen were investigated. Drusen were hypofluorescent in 70% and hyperfluorescent in 22%, including all five patients who were less than 60 years old. No delays in choroidal perfusion were identified in this series of patients, when compared with observed ICG fluorescence characteristics of ciliary artery occlusions.²⁸

ICGA appears to hold great promise in the management of occult choroidal neovascularisation associated with ARM, as it may allow more detailed visualisation of choroidal neovascularisation (CNV) not possible with fluorescein angiography. Eighty seven per cent of patients with exudative ARM presenting to a busy retinal practice had occult or poorly defined CNV, and thus were not amenable to laser photocoagulation therapy.²⁹ Hence, there has been a proliferation of publications on ICGA and occult CNV associated with ARM, as ICGA could possibly convert occult CNV on FFA to well defined CNV on ICGA.³⁰ Yannuzzi and co-workers showed that 118 of 129 consecutive patients with occult CNV associated with ARM (91%) had their CNV confirmed on ICGA.³⁰ Furthermore, 50 of the 129 (39%) had the occult features on fluorescein angiography convert to classic CNV on ICGA. They identified the need to obtain late frames on ICGA after a minimum of at least 30 minutes, believing this was necessary to document the presence of actively proliferating CNV. The ICGA results enabled them to provide laser photocoagulation therapy to 12 patients.³⁰ This rate of conversion from occult to well defined CNV also was documented at the 40% level in two other independent studies.^{31 32} Pilot studies are under way regarding laser photocoagulation for occult CNV and recurrent occult CNV guided by ICGA findings.^{33 34} These results of laser photocoagulation must be considered preliminary as only historical controls are available for comparison regarding visual acuity outcome.

Guyer and co-workers have introduced new terminology into the study of ICGA in occult CNV in ARM – that is, focal CNV versus plaque CNV. Only further natural history studies will show whether this angiographic differentiation is clinically useful.^{35 36} There is a higher correlation between documentation of CNV on FFA and on ICGA than originally reported; the latter publication documenting CNV site on FFA in 86% of their occult CNV series.³⁶ The presence of plaque CNV associated with ARM visualised by ICGA has been documented by a recent clinicopathological correlation.³⁷

The high rates of persistent CNV and recurrent CNV in ARM after laser photocoagulation limits a more favourable visual acuity outcome.^{38–41} ICGA has been proposed as a more effective means of judging adequacy of laser photocoagulation for CNV.⁴² Again, these results have not been reproduced in any controlled setting.

Other innovative developments may bring ICGA to the operating theatre to evaluate the effectiveness of surgical excision of subfoveal choroidal neovascularisation when compared with the preoperative ICGA.⁴³

Leakage of ICG dye into cystoid spaces within the retina in occult CNV associated with ARM has been documented.⁴⁴ Detailed analyses of these images do not permit any conclusions regarding the pathway of ICG movement into these cystic spaces – that is, whether through an incompetent RPE or from overlying retinal vascular changes. Nevertheless, ICG dye in the neurosensory retina is a relative contraindication to diode enhanced laser photocoagulation.⁴⁴

Central serous chorioretinopathy

Perhaps one of the most exciting potential uses of ICG will be in the elucidation of the pathophysiology of various disease processes. While the clinical appearance and natural history of central serous chorioretinopathy (CSC) have been well described, the event which leads to the breakdown of the outer blood-retinal barrier is poorly understood.

Early comparison studies of FFA with ICGA features of CSC did not document any essential differences between these imaging methods.¹⁵ They did, however, show that ICG was able to pass out of the choriocapillaris into the subretinal space.

In Scheider's series of 19 patients with CSC and hyperfluorescence on FFA, 15 of 19 also showed hyperfluorescence on ICGA. This usually correlated well with the FFA pattern – for example, 'smokestack' configuration with each dye.⁴⁵ Two of 19 patients (11%) showed a focal choroidal defect on FFA, whereas 12/19 (63%) showed this feature on ICGA.

The ICG angiograms in Guyer's recent publication on CSC were particularly intriguing.⁴⁶ ICGA in 16 cases of acute CSC confirmed the location of leakage through the RPE in 100% of cases; they appeared to be in the same location as on FFA. However, additional features not seen on FFA were large areas of hyperfluorescence (also previously described by Hayashi¹⁵) and additional areas of hyperfluorescence separate from the active leakage site. These were also seen in the apparently normal fellow eye in some cases. It was suggested that this may represent an increase in hyperpermeability of the choroid which eventually exceeds the capacity of the RPE pump. No delay in choroidal perfusion was identified. Pigment epithelial detachments were seen in 12/16 (75%) and displayed a unique ring pattern on ICGA with central hypofluorescence under the dome of the detachment and a ring of hyperfluorescence at the base. This ring pattern seems very characteristic and may be of particular use in the clinical

setting. It may help differentiate CSC from occult CNV secondary to ARM, by documenting a ring pattern in the eye manifesting symptoms and by identifying areas of focal choroidal hyperfluorescence in the asymptomatic fellow eye. All 13 patients with chronic CSC showed signs of increased hyperfluorescence on ICGA. Similar results were obtained and described by others in subsequent, independent observations.⁴⁷

Inflammatory disorders

There has been considerable controversy regarding the exact nature of changes of the RPE and choroid which result in the characteristic features of acute posterior multifocal placoid pigment epitheliopathy (APMPPE) on fluorescein angiography. Some believe that the early hypofluorescence results from a primary pigment epitheliopathy, while others believe it is due to alterations in choroidal perfusion. ICGA could be particularly useful in this setting to elucidate the underlying pathophysiology by its enhanced ability to characterise the choroidal vasculature. Dhaliwal and co-workers described two patients with newly diagnosed APMPPE who showed characteristic features on FFA; the ICGA performed at the same visit demonstrated a profound delay in generalised choroidal perfusion.⁴⁸ These perfusion defects improved during the review period and also seemed to correlate with an improvement in visual acuity.

The pathogenesis of multiple evanescent white dot syndrome (MEWDS) is seemingly related to a self limited dysfunction of the photoreceptors and RPE. However if this were the case, ICGA in MEWDS should be comparable with an age-matched normal. Ie and co-workers showed that multiple, deep, hypofluorescent areas appeared early and persisted late on ICGA in patients newly symptomatic with MEWDS, and that these hypofluorescent areas resolve over a 6 to 8 week review period.⁴⁹ As most of the clinically evident white dots appeared to correlate with the hypofluorescent areas on ICGA, it was suggested that this represented a change in the choroidal vascular permeability. If the problem were limited to the RPE, the FFA would be abnormal but the ICGA should be normal.

Similarly, ICGA could be useful in identifying choroidal changes not appreciated on FFA in a host of other choroidal inflammatory disorders such as birdshot chorioretinopathy, presumed ocular histoplasmosis syndrome, Vogt-Koyanagi-Harada syndrome, etc. However, only preliminary information is currently available.⁵⁰

Tumours

ICGA has not provided any additional features above and beyond FFA to assist in the diagnosis and management of choroidal tumours – for example, choroidal haemangioma or choroidal melanoma.⁵⁰

Summary and conclusions

New imaging and recording devices which improve temporal and spatial resolution have sparked a renewed interest in indocyanine green angiography. Preliminary results are intriguing, particularly regarding augmentation of our understanding of the pathophysiology of central serous chorioretinopathy and inflammatory disorders of the choroid.

It was hoped that indocyanine green angiography would revolutionise the care of patients with age-related maculopathy by identifying additional patients who might benefit from laser photocoagulation therapy to prevent the

blinding complications of this disorder. All too often, subretinal haemorrhage and detachment of the retinal pigment epithelium limit the identification of well defined choroidal neovascularisation on fluorescein angiography; there should be improved visualisation of choroidal neovascularisation with indocyanine green angiography. While initial studies are promising, no controlled clinical trials have yet identified any benefit of laser photocoagulation therapy in any subgroup of age-related maculopathy when guided by indocyanine green angiography. At present, indocyanine green angiography still remains an investigational tool.

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